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of the

Association for Research in Ophthalmology, Inc.

Second Mid-Winter Meeting

Augusta, Georgia

December 3 and 4, 1959

and

Section Meetings

1959-1960

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CONTENTS

HISTOPATHOLOGY OF THE TRABECULAR MESHWORK IN GLAUCOMA*

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The histopathology of the trabecular meshwork is an important part of glaucoma research since the cause of most glaucomas is suspected in or around this corneoscleral filtration meshwork.[1] This paper is a further contribution to the work that has already been done in this field by many others. The studies of the earlier authors have outlined the typical changes of the trabeculae in the late stages of most of the glaucomas (Sugar[2]). However, there are still controversies on many of the observed details of trabecular pathology and the pathology of the early phases especially of the primary glaucomas is virtually unknown.

The present paper is a collection of typical histologic findings which were made in the trabeculae of many different cases and types of glaucoma with the silver carbonate methods of del Rio Hortega and tangential sectioning of the trabeculae. These special techniques were used in addition to routine sections and staining technique. Many of the observed changes are just a confirmation of the findings of earlier authors. Others fall in the group of changes which are still controversial in their true existence and significance and some of the observed changes are new.

Material and Method

The human eyes used for this study had all been removed surgically and were fixed in formalin or ammonium bromide formalin immediately after enucleation. The clinical history and diagnosis was known in all cases. One half of each eye was imbedded in paraffin and sections from these halves were stained with hematoxylin-eosin. Tangential sections through the area of the filtration angle were made on the freezing microtome from the anterior portion of the other halves of all eyes. These were stained with the unreduced and the threefold methods of the silver carbonate techniques of del Rio Hortega.[3]

All illustrations of this paper are unretouched photomicrographs.

Report and discussion of histologic findings

1. Normal trabeculae

The main difficulty in recognizing early pathology of the trabeculae in glaucoma is that the normal trabeculae of the adult may already show changes that are easily mistaken for the pathology of the glaucoma. Therefore it is necessary for anyone who wants to study the pathology of the trabeculae first to examine normal eyes of all ages to get acquainted with the changes which are usually explained by aging of the normal eye. These changes are known to consist mainly of sclerosis of the trabecular beams, deposition of pigment in the trabeculae and in some cases perhaps of a peculiar granularity (foamy degeneration) of the trabecular collagen in the deep parts of the trabeculae. The first two findings are well known for the papers of Rones,[4] Theobald and Kirk,[5] Teng, Paton and Katzin,[6] Flocks,[7,8] Kurus,[9] and others. The change of granular degeneration of the trabecular beams, however, is still controversial. It has been seen by Teng, Paton and Katzin.[6] Some authors suspect it to be an artefact (Ashton[10]).

Another reason for confusion between normal findings and pathologic changes of the trabeculae seems to be the fact that eyes with intraocular tumors—mostly malignant melanomas of the choroid—have been used by many as "normal" eyes as far as the trabeculae are concerned. And the trabeculae

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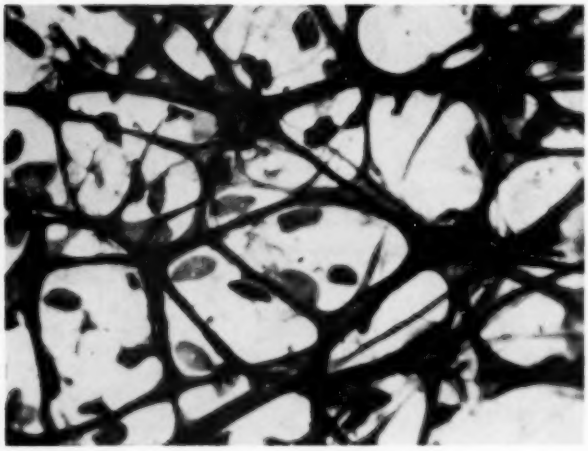

Fig. 1 (Wolter). High-power view of uveal meshwork of normal eye of two-month-old child. The trabecular beams are surrounded by endothelial cells. (Tangential section, Hortega stain, photomicrograph.)

of these eyes has been compared with that of glaucomatous eyes. It is now agreed, however, that the trabeculae of most eyes with malignant melanomas show definite pathology.[10] This goes along with the clinical observation of Becker[10] that eyes with malignant melanomas have flat tonographic tracings in much higher instances than normal eyes.

Figure 1 shows a part of the deep uveal meshwork of the trabeculae of the normal eye of a two-month-old child. The collagen fibers of the trabeculae in this case from very delicate meshes with large spaces. Endothelial cells with oval nuclei are seen lining and in some areas bridging these spaces. The scleral part of the trabeculae in this child showed much the same structure with only slightly coarser trabecular beams while the innermost trabeculae of the uveal portion (pectinate ligament) were even more delicate than the ones in Figure 1 (Wolter[11]).

Figure 2 represents a view of a tangential section through the limit between uveal and scleral portions of the trabeculae of the eye of a child 16 months of age. However, this eye contained a large retinoblastoma. The trabecular beams in this eye were somewhat

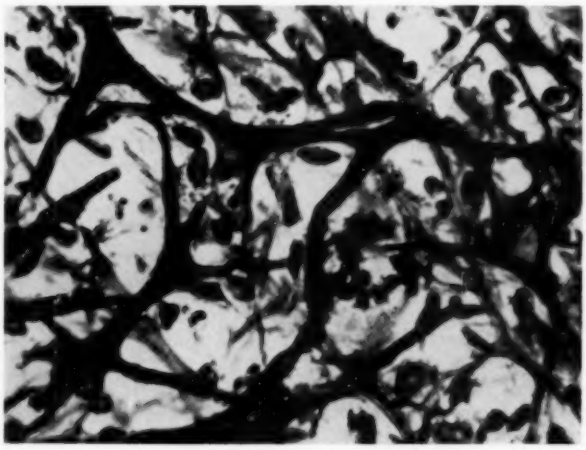

Fig. 2 (Wolter). High-power view of the trabecular meshwork at the limit between uveal and scleral meshwork of the eye of a 16-month-old child with advanced retinoblastoma. The dark-stained trabeculae are of the uveal meshwork. The light-stained trabeculae are of the scleral meshwork. All trabeculae are swollen and the number of endetholial nuclei appears increased. (Tangential section, Hortega stain, photomicrograph.)

coarser all through the trabecular meshwork and there seemed to be a comparative increase and swelling of the endothelial cells. Many of these cells contained pigment granules.

Figure 3 shows a low power view of the filtration angle of the eye of a 40-year-old woman that contained a very small, flat choroidal melanoma of spindle A cell type. This can—after all that I know now—be considered as a normal angle of an adult. The trabeculae (a) Schlemm's canal (b) and the adjacent membrane of Descemet (c) with many Hassall-Henle bodies can be well recognized. The plane of this section very well shows that the trabeculae are actually not round fibrillar beams but rather broad sheaths of collagen tissue with many perforations in them. Such sheaths are arranged in overlapping layers and the large openings in the area of the uveal part of the trabecular funnel down to small passageways in the

Fig. 3 (Wolter). Low-power view of the whole filtration angle of a 40-year-old woman with a small choroidal melanoma: (a) the trabeculae, (b) Schlemm's canal, (c) Descemet's membrane with Hassall-Henle bodies on it. (Tangential section, Hortega stain, photomicrograph.)

Fig. 4 (Wolter). Higher-power view of the same trabeculae which are seen in Figure 3. This is an example of the normal trabeculae of an adult. (Tangential section, Hortega stain, photomicrograph.)

medial wall of Schlemm's canal.[12] The decrease of the size of the perforations in the trabecular sheaths as we move towards the canal of Schlemm becomes very obvious if we look at the same trabeculae with higher power (fig. 4). The highest power shows that a peculiar shrinkage has occurred in many trabeculae of the uveal portion (fig. 5). This indicates two things: (1) that the trabeculae must normally be under a certain tension and (2) that the uveal trabeculae are elastic. I believe that this irregular shrinkage is caused by release of the tension that is normally exerted on the trabeculae by the action of the ciliary muscle. It is said in the textbooks that the uveal meshwork lacks the inner elastic layer which is found in the scleral meshwork. However, the concept that the trabeculae may be opened and closed by motion of the scleral spur caused by action of ciliary muscle fibers can only be accepted if it is agreed that all trabecular

Fig. 5 (Wolter). High-power view of the inner fibers of the uveal trabecular network seen in Figure 3 and 4 shows shrinkage (arrow) of trabecular beams. (Tangential section, Hortega stain, photomicrograph.)

beams are elastic (Rohen,[13] Garron,[10] Ashton[10]). The highest power applied to the area of the scleral meshwork (fig. 6) shows the regular arrangement of the collagen fibrils in the sheaths of the trabeculae as I consider it normal in an adult. It must be added that a normal number of endothelial cells was seen in this trabecular meshwork. However, the stain used in the photographed section did not show them.

Figures 7 and 8 are taken from a tangential section of the trabeculae of the eye of a 31-year-old man with a large spindle-A cell melanoma of the choroid. Both pictures show the trabecular beams to be thickened and the perforations to be decreased in size. Figure 8 shows that there is not only thickening of the trabeculae but also a peculiar granularity of the collagen of the trabecular beams. It may be emphasized that this eye was fixed by injection into the globe immediately after surgical removal. I have no doubt that this peculiar granularity of the trabecular collagen represents the same change that was described by Teng, Paton and Katzin[6] and by Flocks[7,8] under the term of foamy appearance of the trabeculae.

Figures 9 and 10 show areas of a tangential section of the trabeculae of the completely normal eyes of a 78-year-old man which was removed because of a basal cell carcinoma in the orbit. Thickening and sclerosis of the trabecular beams but no granularity of the collagen were seen in the uveal (fig. 9) and in the scleral (fig. 10) meshwork.

Many of the eyes with and without glaucoma of adult and old people allowed for a very interesting observation. Dense hyaline bodies (Hassall-Henle bodies) were found on Descemet's membrane adjacent to the trabeculae (fig. 11, also fig. 3). This was interesting since it seemed that the size and density of these hyaline bodies was much

Fig. 6 (Wolter). Structure of the deep scleral meshwork at high power from the same trabecular network as seen in Figure 3. The bundles of collagen in the trabecular beams are well visible. (Tangential section, Hortega stain, photomicrograph.)

Fig. 7 (Wolter). Advanced sclerosis and some granularity of the trabecular beams of a 31-year-old man with a large choroidal melanoma. (Tangential section, Hortega stain, photomicrograph.)

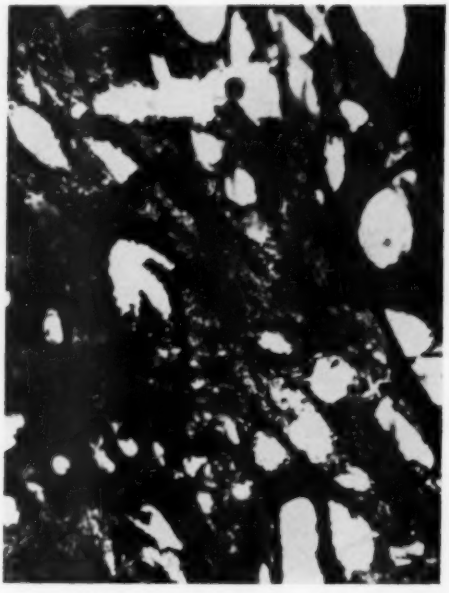

Fig. 8 (Wolter). Extensive granularity of the collagen of the scleral trabeculae close to Schlemm's canal in the case of the advanced choroidal melanoma in the eye of a 31-year-old man. (Tangential section, Hortega stain, photomicrograph.)

greater in those eyes that showed advanced thickening (sclerosis) of the trabeculae than in eyes without such sclerosis. Figure 12 demonstrates that the hyaline warts on the peripheral membrane of Descemet in the eye of a 72-year-old woman were actually seen at the very limit of the trabecular endothelium to the corneal endothelium. There is not much doubt that the hyaline warts of the peripheral cornea are formed by the corneal endothelium. The fact that sclerosis of the trabeculae and extensive Hassall-Henle bodies seem to occur together might suggest that trabecular sclerosis may also be a product of deposition from the related trabecular endothelium.

The above cases were demonstrated to show that:

1. The collagen beams of the trabeculae of

Fig. 9 (Wolter). View of a section through the uveal meshwork of the normal eye of a 78-year-old man. Some sclerosis can be seen. (Tangential section, Hortega stain, photomicrograph.)

Fig. 10 (Wolter). View of the scleral meshwork of the normal eye of a 78-year-old man. Extensive sclerosis but no granularity of the collagen are seen. (Tangential section, photomicrograph, Hortega stain.)

a small child are very delicate and that thickening (sclerosis) of the trabeculae occurs through life.

2. A special type of granularity (foamy degeneration) of the collagen of the trabecular beams is often seen in the trabeculae of pathologic eyes. However, it does not seem to occur in the trabeculae of well-fixed normal eyes—even not in advanced age.

3. That the trabeculae of eyes with advanced melanoma of retinoblastoma often exhibits trabecular pathology and cannot be considered normal. This pathology seems to be composed of early and extensive trabecular sclerosis, extensive pigment deposition, endothelial swelling and proliferation and granularity of the trabecular collagen.

4. The development of hyaline warts on the the periphery of Descemet's membrane seems to go parallel to the sclerosis of the trabeculae. Both changes may be caused by deposition of hyaline substance by the endothelium.

The trabecular changes in the following case are interesting because of the rarity of the disease. A case of primary amyloidosis was examined and showed histologically extensive deposition of amyloid in the vitreous and in the wall of intraocular blood vessels. The collagen structure of the trabeculae of both eyes was normal. A view of the deep trabeculae at high power is seen in Figure 13. The endothelium, however, showed extensive swelling and hylanization. It must be emphasized that these hyalinized cells in the trabecular spaces reacted histologically as

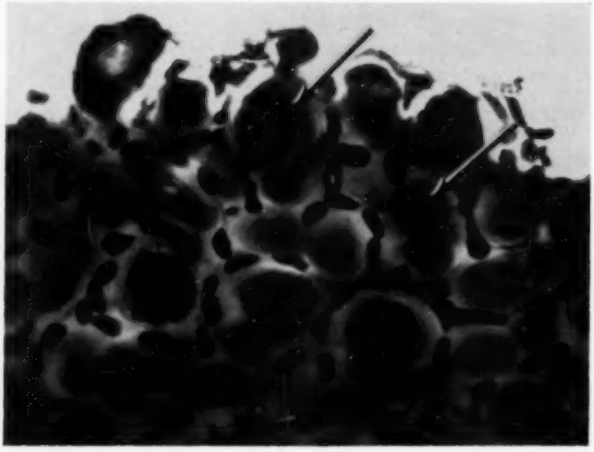

Fig. 11. (Wolter). Densely accumulated Hassall-Henle bodies on the posterior surface of the peripheral cornea in the normal eye of a 78-year-old man. The hyaline bodies (arrows) are surrounded by the compressed cells of the peripheral corneal endothelium. (Tangential section, Hortega stain, photomicrograph.)

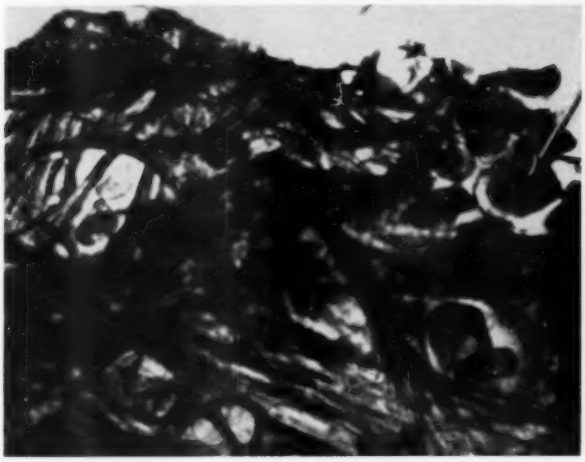

Fig. 12 (Wolter). Corneal margin of the trabecular meshwork of the eye of a 72-year-old woman with absolute glaucoma. Part of the trabecular meshwork is seen in the left side of the picture. Hassall-Henle bodies (arrow) are found on the cornea right next and virtually within the trabecular meshwork. (Tangential section, Hortega stain, photomicrograph.)

hyalin and gave negative staining reactions for amyloid.

2. Pathology of open-angle glaucoma

Five eyes with open-angle (chronic simple) glaucoma were studied with tangential sections and silver carbonate staining. Three of these eyes were of the absolute stage. Two eyes, however, were removed from a 78-year-old patient with well studied open-angle glaucoma who died of rectum carcinoma.

Fig. 13 (Wolter). View of the trabecular meshwork of the eye of a patient with primary amyloidosis. The trabeculae are about normal. Large hyaline bodies (arrow) are seen in the intertrabecular spaces. (Tangential section, Hortega stain, photomicrograph.)

Figures 14 to 22 were taken from tangential sections of the trabeculae of the eye of a 42-year-old male with absolute open-angle glaucoma. Figure 14 shows a part of the inner portion of the uveal meshwork (pectinate ligament).

The important change seen in this picture is that the trabecular spaces are not empty as they are in normal eyes and just lined by small endothelial cells. Here most of the trabecular spaces are filled by a very slightly stained homogeneous substance. This substance seems to represent the endothelial protoplasm since the endothelial nuclei are seen in the middle of it (fig. 14). Some trabecular spaces seem to be completely filled with the protoplasm of the swollen endothelial cells. Others still have small openings (b in fig. 14).

As we look at the deeper parts of the trabeculae (fig. 15), we find in addition a tremendous increase in the number of cellular nuclei. All the nuclei seem to belong to cells of the same kind and they all look like endothelial cells. Therefore we think that

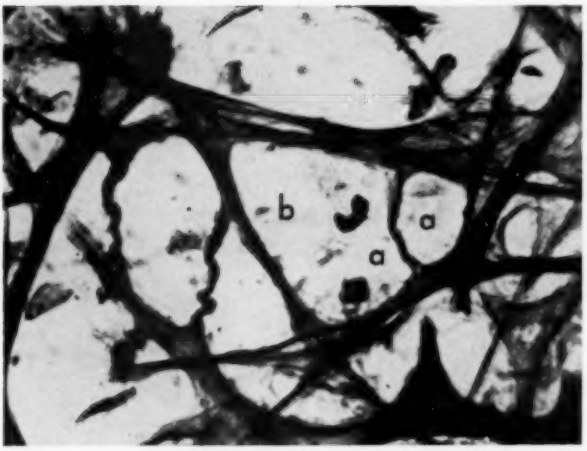

Fig. 14 (Wolter). View of a section through the uveal meshwork in the eye of a 42-year-old man with absolute open-angle glaucoma. The endothelium is swollen (a) and fills most of the trabecular spaces. Openings (b) are seen in some areas. (Tangential section, Hortega stain, photomicrograph.)

this is true proliferation of the trabecular endothelium. The scleral portion of the trabecular meshwork in this case of absolute open-angle glaucoma showed very extensive thickening of the trabeculae in addition to the endothelial proliferation (fig. 16). This deep intertrabecular spaces.

Figure 16 shows these narrowed trabecular spaces filled with densely arranged endothelial nuclei. There was also deposition of pigment in all parts of this trabeculae.

Figure 17 shows pigment granules in the swollen endothelium of the uveal trabeculae.

Figure 18 is a high-power view of one of the innermost trabecular beams of this case with endothelial cells attached to it. These endothelial cells appear rather normal in shape but they have pigment granules in their protoplasm.

The deeper parts of the trabecular meshwork of this eye contained pigment not only as diffuse granules but there were branching cells in the trabeculae which were densely filled with pigment (figs. 19 and 20). It is possible to stain these pigment-containing cells of the trabecular meshwork without staining the collagen of the trabeculae. These cells then looked just like melanocytes (chro-

Fig. 15 (Wolter). View of a section through the deeper parts of the uveal meshwork in the eye of a 42-year-old man with open-angle glaucoma. There is extensive proliferation of the trabecular endothelium and some sclerosis of the trabecular beams. (Tangential section, Hortega stain, photomicrograph.)

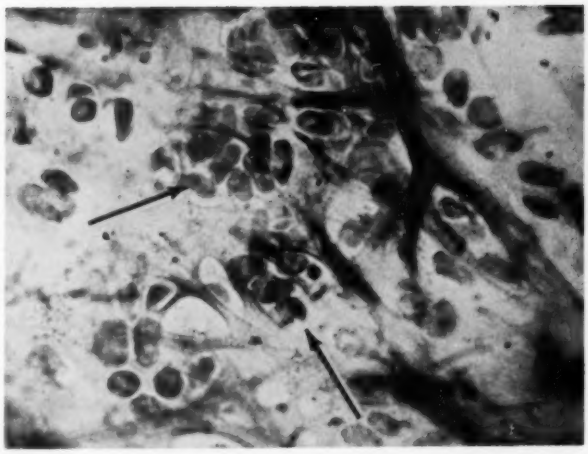

Fig. 16 (Wolter). View of the scleral meshwork in the eye of a 42-year-old man with absolute open-angle glaucoma. There is extensive sclerosis and decrease of the size of the perforation in the trabecular sheaths. These spaces are densely filled by endothelial cells (arrows). (Tangential section, Hortega method, photomicrograph.)

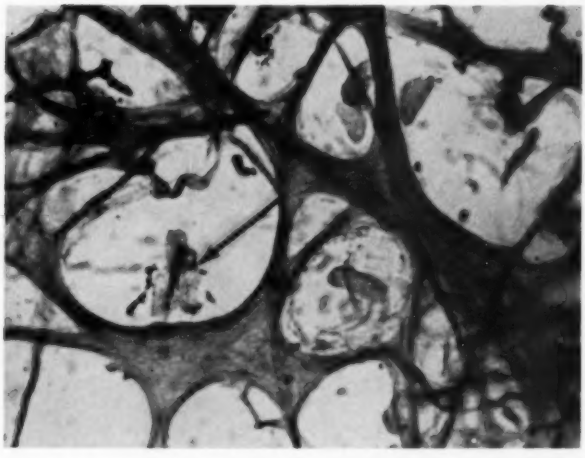

Fig. 17 (Wolter). Pigment granules are seen in the endothelial cells of the uveal meshwork of an eye of a 42-year-old patient with absolute open-angle glaucoma. (Tangential section, Hortega method, photomicrograph.)

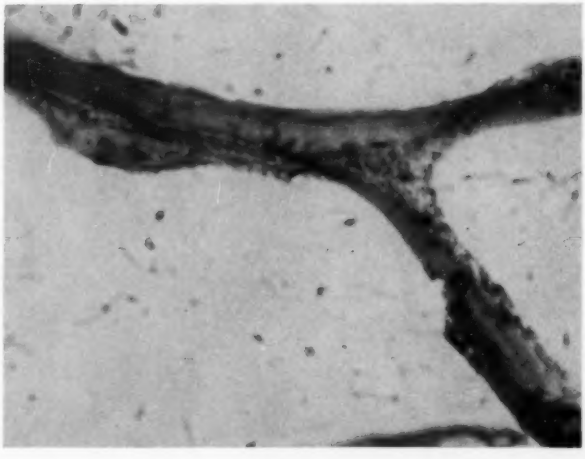

Fig. 18 (Wolter). One of the innermost trabecular beams of the uveal meshwork of the eye of an 42-year-old male with absolute open-angle glaucoma. Pigment granules are seen in the protoplasm of endothelial cells which are surrounding the trabecular beam. (Tangential section, Hortega stain, photomicrograph.)

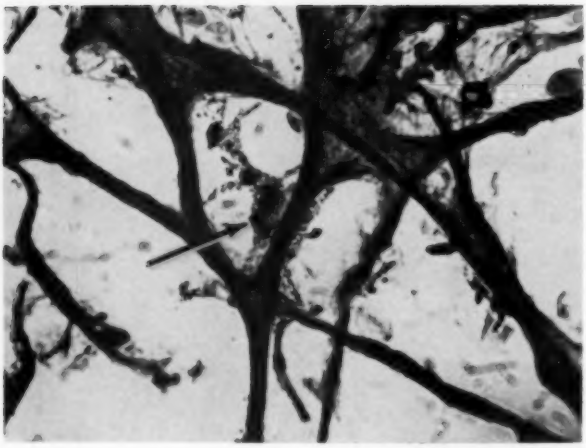

Fig. 19 (Wolter). Uveal trabeculae of the eye of a 42-year-old man with open-angle glaucoma with pigment containing cells (arrow). (Tangential section, Hortega stain, photomicrograph.)

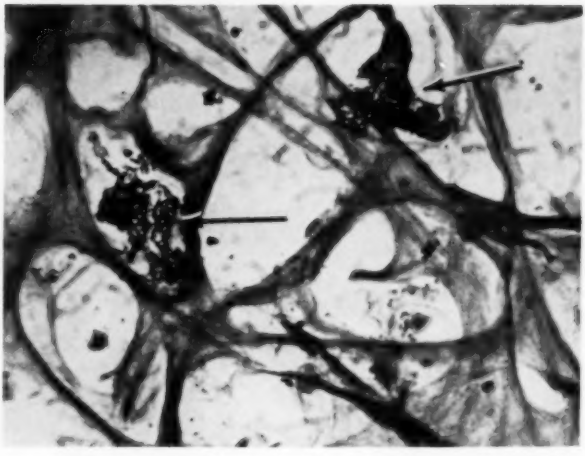

Fig. 20 (Wolter). Cells filled with pigment (arrows) in the trabeculae in absolute open-angle glaucoma. (Tangential section, Hortega stain, photomicrograph.)

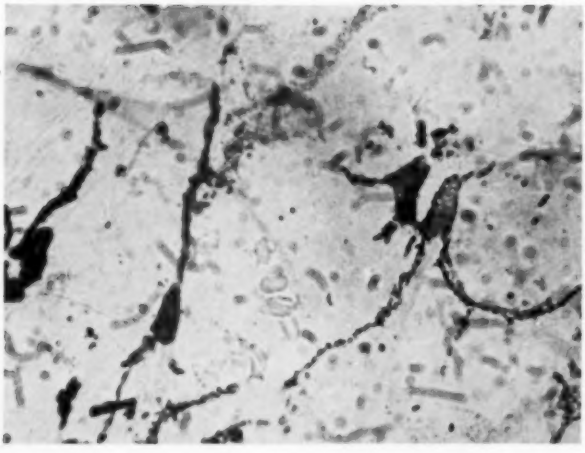

Fig. 21 (Wolter). Trabecular network of the eye of a 42-year-old man with open-angle glaucoma. The trabeculae are unstained, only the pigment containing cells are visible. (Tangential section, Hortega stain, photomicrograph.)

matophores) as known from the iris or ciliary body (fig. 21). I do not know whether the pigmented cells of the trabeculae are melanocytes or cells of the trabecular endothelium which have phagocytized pigment.

The deep parts of the corneoscleral trabecular meshwork adjacent to Schlemm's canal showed the most extensive proliferation of endothelial cells (fig. 22). It can be demonstrated that these cells are imbedded in a dense meshwork of very delicate argyrophilic fibers (fig. 23). This proves that these cells are not just loosely accumulated there but they must represent dense tissue which is fixed in this location and must block the current of fluid into Schlemm's canal.

Figure 24 shows the more blood-vessel like endothelium of the inner wall of Schlemm's canal which does not seem to have taken part in the proliferation of the trabecular endothelium. Figures 23 and 24 were taken from tangential section of the trabecular meshworks of a 78-year-old woman who was treated for three or four years for open-angle glaucoma. One of her eyes with absolute glaucoma was available for this study.

Fig. 22 (Wolter). Proliferation of endothelial cells at the inner wall of Schlemm's canal in absolute open-angle glaucoma. (Tangential section, Hortega stain, photomicrograph.)

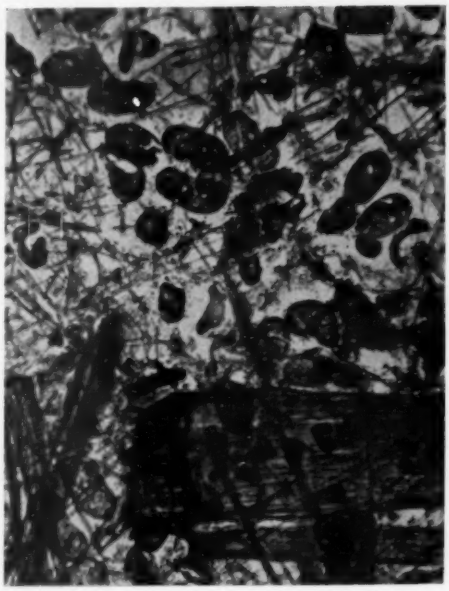

Fig. 23 (Wolter). Nuclei of cells at the inner trabecular wall of Schlemm's canal of the eye of a 78-year-old woman with open-angle glaucoma. A dense fiberwork of argyrophil fibrils is seen to fix the cells. (Tangential section, Hortega stain, photomicrograph.)

Figures 25 to 27 show the changes in the structure of the trabeculae in an aphakic eye of a 70-year-old patient that was removed because of bullous keratopathy in absolute open-angle glaucoma. The lower power view (fig. 25) shows the whole filtration angle in a tangential section. Schlemm's canal (a) is open but appears rather small. The trabeculae (b) are sclerotic. This sclerosis of the trabecular beams is even more impressive when seen with higher power (fig. 26). The endothelium in this case showed also proliferation and was filled with pigment granules but the endothelium remained almost unstained in the section here photographed. In addition to the sclerosis there was granularity of the collagen seen in the

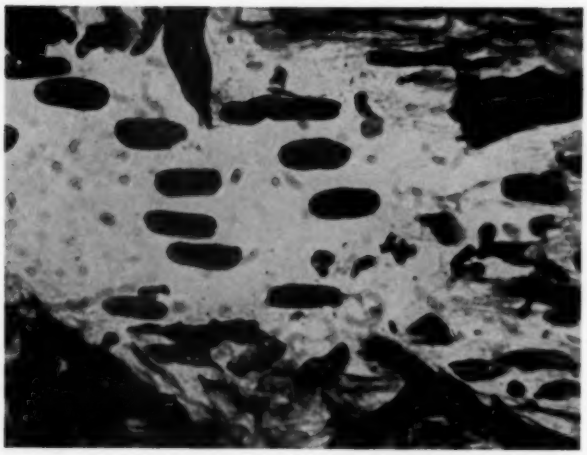

Fig. 24 (Wolter). The endothelium of the inner wall of Schlemm's canal in the eye of a 78-year-old woman with absolute open-angle glaucoma. These cells have not taken part in the proliferation of the trabecular endothelium. (Tangential section, Hortega stain, photomicrograph.)

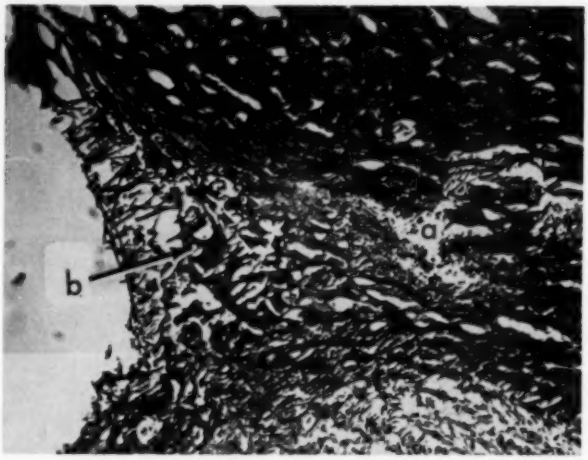

Fig. 25 (Wolter). Low-power view of the filtration angle of a 70-year-old man with absolute open-angle glaucoma: (a) Schlemm's canal, (b) trabeculae. (Tangential section, Hortega stain, photomicrograph.)

Fig. 26 (Wolter). High-power view of the sclerotic trabeculae seen in Figure 25. (Tangential section, Hortega stain, photomicrograph.)

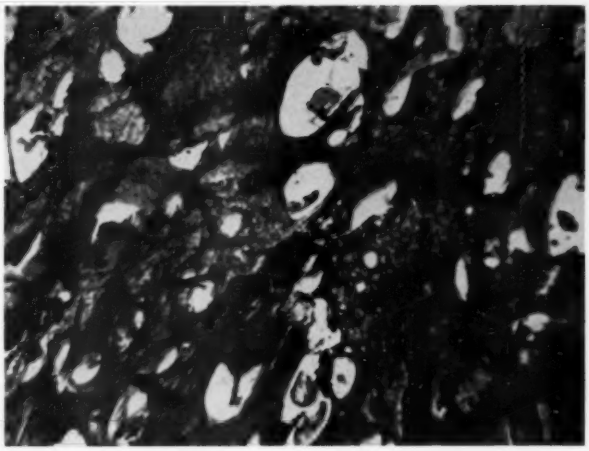

Fig. 27 (Wolter). High-power view of the trabeculae seen in Figure 25. This area next to Schlemm's canal shows advanced granularity of the trabecular collagen. (Tangential section, Hortega stain, photomicrograph.)

deep parts of the scleral trabeculae (fig. 27).

Both eyes with open-angle glaucoma of a 78-year-old man who died of rectum carcinoma* could be examined in this study. He was treated in this clinic for five years and never had surgery. He had still a vision of O.D., 6/25, and O.S., 6/12, when he died. This was partly explained by cataracts. His fields showed only slight glaucomatous changes. This case of a relatively early stage of open-angle glaucoma showed advanced sclerosis of its trabeculae and extensive proliferation of the trabecular endothelium. However, there was no granularity of the collagen seen in this case (Wolter[13]). This may indicate that sclerosis and proliferation of the trabecular endothelium are part of the pathologic picture seen in earlier phases of open angle glaucoma while granularity of the collagen might be a late change caused by the long-standing glaucoma (Flocks[7,8]).

The nerve-fiber stains done on the tangential sections of the trabeculae of eyes with open-angle glaucomas were of special interest. Peculiar nerve-fiber changes were seen in different stages of their development in all my cases of open-angle glaucoma. These changes were not seen in any other eyes—normal or with other types of glaucoma.

It is well known from earlier studies of other authors and myself that the normal human trabeculae has a rich nerve supply.[9,11,13–15] The nerve fibers originate in the ciliary nerve plexus and I agree with Holland, von Sallmann and Collins[14,15] that they end in the trabecular endothelium without forming any special end-apparata.

Figures 28, 29 and 30 were taken from tangential sections of the trabeculae of the eyes of the above mentioned 78-year-old man who died of rectum carcinoma. The trabecular meshwork of both of these eyes showed in addition to the trabecular sclerosis and the proliferation of the endothelium very extensive nerve fiber pathology. In some parts of the trabecular meshwork the nerve fibers were just slightly thickened and irregular in their caliber (fig. 28). In other areas interruption of nerve fibers was seen with the formation of bizarre terminal swellings. However, there were not only degenerative but also reactive nerve fiber changes. New growth of thin and irregular neurite branches was seen to have occurred from the ends of interrupted nerve fiber stumps. This had resulted in the formation of nerve fiber structures that looked somewhat like trees

* These are the only eyes of this study that were not removed surgically and fixed immediately. However, these eyes were removed and fixed about four hours after death and showed no autolytic changes in other parts of the eyes.

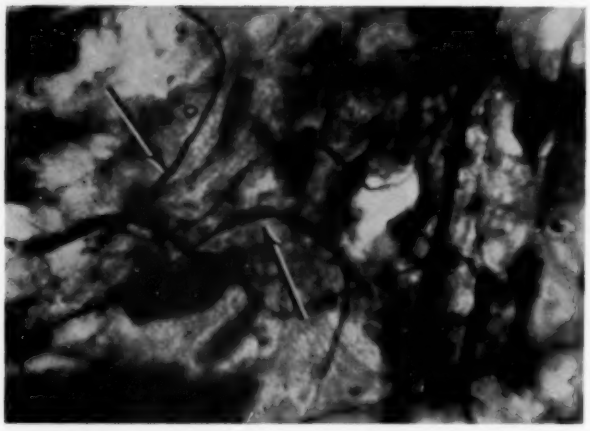

Fig. 28 (Wolter). Nerve fibers in the trabeculae of an eye of a 78-year-old man with open-angle glaucoma. The nerve fibers in this area (arrows) show only slight pathology—swelling and irregularity of caliber. (Tangential section, Hortega stain, photomicrograph.)

and had coiled up and partially swollen branches (fig. 29). These formations looked exactly like the "sensory nerve apparata" which Kurus[9] described in the nomal human trabeculae. I have no doubt that these represent the product of chronic nerve-fiber pathology which is typically seen in open-angle glaucoma. In other areas of the trabeculae of the same eyes the central stumps of the interrupted nerve fibers showed huge cell-like terminal swellings of nerve substance (fig. 30).

A more extensive demonstration of the neuropathology of the trabeculae of both eyes of this 78-year-old patient with open-angle glaucoma is published elsewhere.[13] Basically the same nerve-fiber changes were seen in two cases of absolute open-angle glaucoma. However, in these cases there were only few nerve fibers left in the trabeculae while most of them had disappeared completely. I am certain that the nerve-fiber changes seen in these cases are not artefacts. They represent not only degeneration but also pathologic reaction of the nerve fibers as known from experiments and the pathology of nerves of other human tissues. Such changes cannot be explained by autolysis after death. The type of nerve-fiber pathology found in these few cases of open-angle glaucoma indicates that the damage causing them must be very slowly progressive and chronic

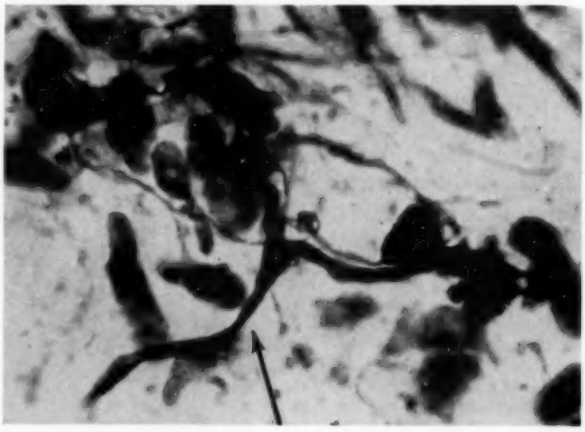

Fig. 29 (Wolter). Pathologic treelike formation at the end of an interrupted nerve fiber in the trabeculae of a 78-year-old man with open-angle glaucoma (arrow). (Tangential section, Hortega stain, photomicrograph.)

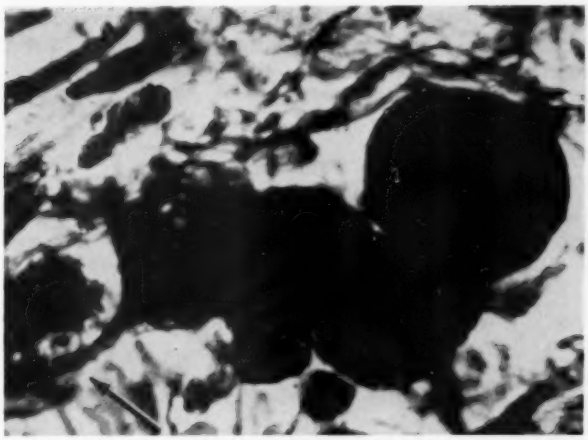

Fig. 30 (Wolter). A bizarre extremely large terminal swelling of an interrupted nerve fiber (arrow) in the trabecular meshwork of a 78-year-old man with open-angle glaucoma. (Tangential section, Hortega stain, photomicrograph.)

as to allow for the extensive reactive changes. There is no indication in the slides of my cases to show whether the nerve-fiber pathology of the trabecular meshwork is of primary or secondary nature.

In summarizing the findings in the demonstrated cases of open-angle glaucoma the following changes in the trabecular meshwork can be listed: (1) swelling and proliferation of the trabecular endothelium, (2) pigment deposition in and around the trabecular endothelium, (3) sclerosis and in some cases granularity of the collagen of the trabecular beams, and (4) chronic degenerative and reactive nerve-fiber changes.

It must be emphasized that of these changes only the proliferation and swelling of the trabecular endothelium and the nerve-fiber pathology appear to be in any way typical for open-angle glaucoma. The proliferation seems to be especially important since this change is just opposite to that of aging which goes along with a decrease of the number of endothelial cells in the trabeculae. The sclerosis and pigment deposition can be found in any normal trabeculae. The granularity of the collagen of the trabeculae may be seen in any old pathologic process involving the trabecular meshwork.

Proliferation and swelling of the trabecular endothelium in open-angle glaucoma has been described before by Teng, Paton and Katzin,[6] Rohen and Unger,[16] Flocks,[7,8] and Kornzweig, Feldstein and Schneider.[17] The just-described nerve-fiber pathology of open angle glaucoma (Wolter[13]) has, to my knowledge, not been demonstrated before. I believe that the swelling and proliferation of the endothelium and the nerve-fiber degeneration are important findings in the trabeculae of eyes with open-angle glaucoma. The other listed changes seem to be secondary and probably caused by the glaucoma.

The fact that the trabecular endothelium in open-angle glaucoma appears swollen and to be filled with some homogeneous intraprotoplasmatic substance is of great interest. It would be important to know what the substance in these cells is. Could it be acid mucopolysaccharides (Zimmerman[18])?

3. Pathology of closed-angle glaucoma

I have been unable as yet to examine the eye of a patient with an early stage of angle-closure glaucoma. Cases of absolute stages of angle-closure of the primary type have been seen. However, these eyes do not seem to show anything that might help to solve the problem of the cause and nature of the primary angle-closure glaucoma.

The trabecular pathology in the cases of absolute primary angle-closure glaucoma was found to be composed of the following changes: atrophy of the trabecular endothe-

lium, complete atrophy of the trabecular nerves, and collapse of the trabecular network. In most cases it was surprising to see that the collapsed trabecular beams were still rather well preserved. There was sclerosis and sometimes—but not always—granularity of the collagen. The sclerosis in all cases could be explained by age. Most of the trabecular endothelium was missing in our cases and the endothelium was completely gone in two cases. The most extensive atrophy of the endothelium is always found in the inner parts of the trabecular network. The endothelium of Schlemm's canal and that next to it was usually found to have survived. The lumen of Schlemm's canal appeared obliterated in most cases. I explain the destruction of the trabecular endothelium by the fact that the endothelium looses its source of nutrition with the block of the flow of aqueous by the angle closure. The survival of the endothelium in Schlemm's canal can be explained by back-flow of nutritional fluid from the side of the aquous veins.

It is not surprising to find that all nerve fibers were gone in the trabeculae of absolute cases of angle-closure glaucoma. The nerve fibers are, of course, much more vulnerable to any type of direct damage and therefore would be expected to degenerate much before the trabecular endothelium. The stumps of the nerves that have supplied the trabeculum in these cases can be demonstrated in the ciliary plexus or in the long ciliary nerves. Figure 31 shows two stumps of such degenerating nerve fibers in the ciliary nerve of an eye with absolute closed angle glaucoma. Figure 32 shows the nerve stumps with coarse terminal swellings and surrounded by lipids at higher power.

4. Pathology of secondary glaucoma

Figure 33 represents the low-power view of the trabecular meshwork of an eye with absolute phacolytic glaucoma. The routine stains of the trabeculae of this eye had revealed many phagocytes in the trabeculae. The silver stains showed the trabeculae to be otherwise about normal for the 75-year-old patient. Blood was seen in the canal of Schlemm. The fact that no pathology was found in the trabeculae of this case—except for the phagocytes in the trabeculae and advanced sclerosis—may explain why phacolytic glaucoma is usually cured after removal of the hypermature lens.[19]

Many cases of secondary (hemorrhagic) glaucoma following occlusion of the central retinal vein or artery[20] were studied with tangential sections and silver carbonate

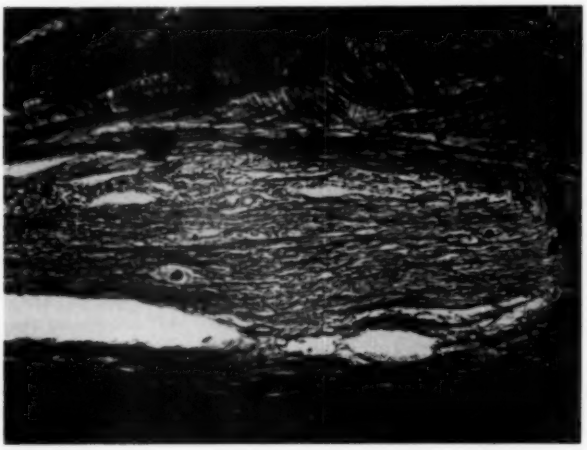

Fig. 31 (Wolter). Ciliary nerve in the sclera of an eye with absolute angle-closure glaucoma. Degenerating nerve fibers are seen all through the nerve. (Tangential section, Hortega stain, photomicrograph.)

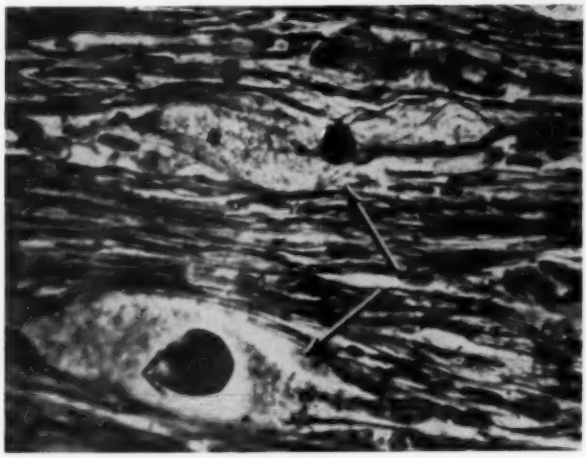

Fig. 32 (Wolter). High-power view of a part of the nerve seen in Figure 31. Two interrupted nerves with terminal swellings (arrows) are seen. (Frozen section of sclera, Hortega stain, photomicrograph.)

stain. The pathology of the trabecular network in these cases was found to be rather uniform.

Figures 34 to 38 were taken from tangential sections of the trabecular meshwork of an eye with absolute hemorrhagic glaucoma in a 77-year-old woman. The angle in this eye was open but there was extensive rubeosis iridis and fibrovascular tissue could be seen to extend into the trabeculae in the routine sections. Figure 34 shows the innermost portion of the uveal meshwork. Early granularity of the collagen of the trabecular beams is clearly visible. A view of the deeper trabecular meshwork is given in Figure 35. This exhibits in addition to the granularity of the collagen a tremendous increase of cellular nuclei in the spaces of the trabecular meshwork. Most of these cells were endothelial cells. However, there were also mononuclear inflammatory cells, fibroblasts and erythrocytes.

Figure 36 shows an accumulation of erythrocytes in this trabecular network. Two branching thin-walled blood vessels are seen to run within the trabecular meshwork in

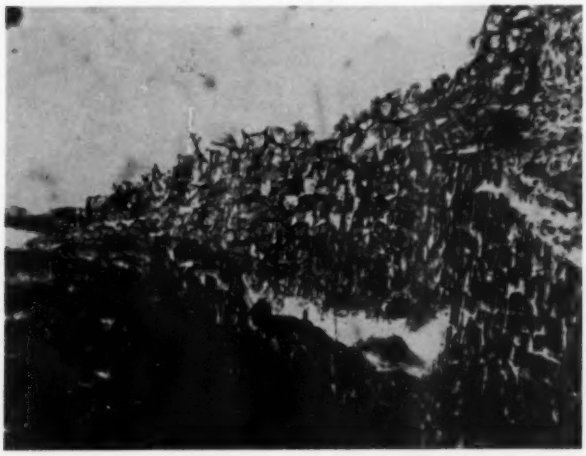

Fig. 33 (Wolter). The filtration angle of an eye with phacolytic glaucoma. The trabeculae are rather sclerotic but show no granularity of their collagen. Blood is seen in Schlemm's canal. (Tangential section, Hortega stain, photomicrograph.)

Fig. 34 (Wolter). Section through the inner part of the uveal trabeculae of a 77-year-old man with absolute hemorrhagic glaucoma. There is early granularity of the trabecular collagen. (Tangential section, Hortega stain, photomicrograph.)

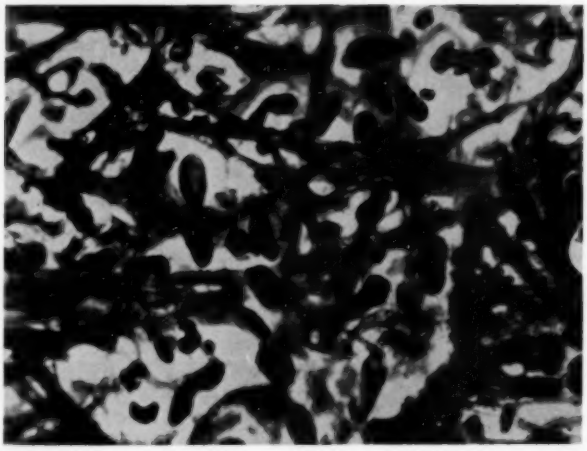

Fig. 35 (Wolter). Section through the deeper uveal meshwork of the same trabecular meshwork as seen in Figure 34. Extensive proliferation of the trabecular endothelium is the main pathology seen in this area (Tangential section, Hortega stain, photomicrograph.

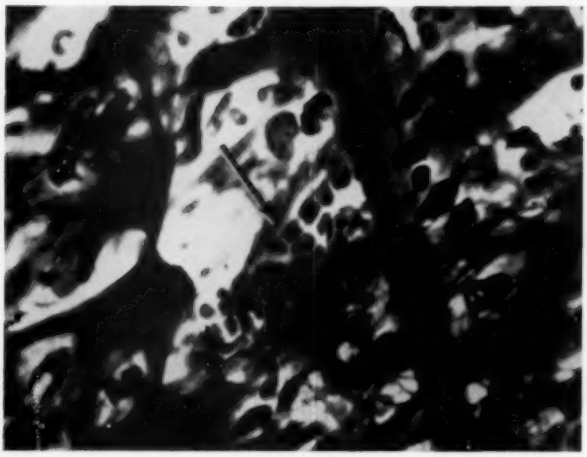

Fig. 36 (Wolter). An accumulation of blood in the sclerotic trabeculae of a 77-year-old patient with absolute hemorrhagic glaucoma. (Tangential section, Hortega stain, photomicrograph.)

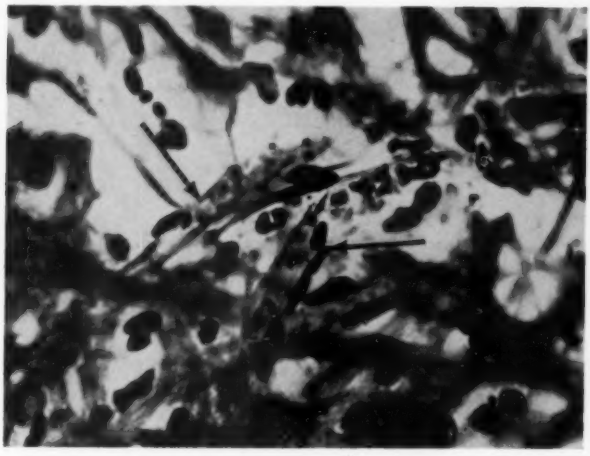

Fig. 37 (Wolter). Branching capillaries containing blood in the trabeculae of a 77-year-old patient with absolute hemorrhagic glaucoma. (Tangential section, Hortega stain, photomicrograph.)

Figure 37. The finding of blood vessels was never made by me in any type of primary glaucoma. However, blood vessels in the trabecular structures can be seen in cases of old ocular trauma or inflammation with or without glaucoma. The high degree of granularity of the collagen of the scleral meshwork is demonstrated in Figure 38. This granularity goes along with definite thickening of the trabecular beams and with narrowing of the intertrabecular spaces.

Figures 39 and 40 are taken from the trabecular meshwork of an eye of a 50-year-old woman with absolute hemorrhagic glaucoma in diabetes mellitus. A lake of blood adjacent to the inner trabeculae is seen in Figure 39. Figure 40 shows the extensive neovascularization of deeper parts of the trabecular meshwork in the same case.

Only very few surviving nerve fibers were found in the trabeculae of the cases of hemorrhagic glaucoma all of which were in the absolute phase. Very often, however, the stumps of degenerating nerve fibers are seen in the ciliary body and in the ciliary nerves. Figure 41 shows the stump of such a degenerated nerve fber directly posterior to the trabecular meshwork in the ciliary mus-

Fig. 38 (Wolter). Section through the scleral trabeculae of an eye of a 77-year-old man with absolute hemorrhagic glaucoma. There is extensive granularity of the trabecular collagen. (Tangential section, Hortega stain, photomicrograph.)

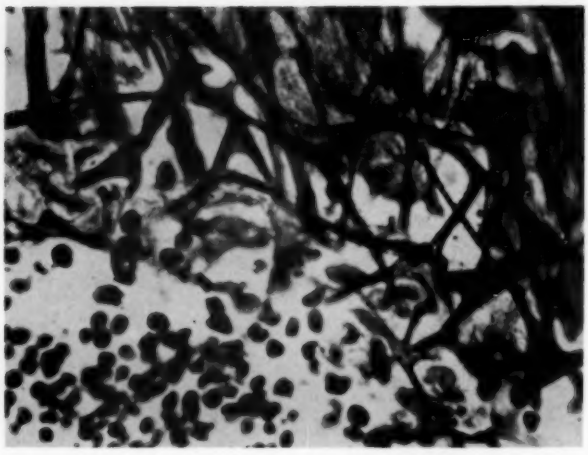

Fig. 39 (Wolter). Blood on the inside of the trabecular meshwork in the eye of a 50-year-old woman with hemorrhagic glaucoma. (Tangential section, Hortega stain, photomicrograph.)

cle. This stump is swollen as can be seen by comparison to the delicate nerve fibers innervating the smooth ciliary muscle fibers around the swollen stump. This was seen in the eye of a 77-year-old woman with hemorrhagic glaucoma.

In summarizing it can be said that the typical pathology of secondary (hemorrhagic) glaucoma following occlusion of central retinal vessels is composed of increased cellularity and neovascularization as main features. It appears to me that the neovascularization alone would in many cases not explain why the outflow had been decreased. However, the extensive proliferation of the trabecular endothelium and the additional accumulation of other cells in the trabeculae which were present in all my cases would explain the clinically known obtruction of the trabecular meshwork in these cases. All cases also exhibited extensive sclerosis and granularity of the trabeculae. In the late stages of hemorrhagic glaucoma angle closure and collapse of the trabeculae often complicates the histologic picture.

This is about all that I now know of the pathology of the trabecular meshwork in glaucoma. There are some rather interesting

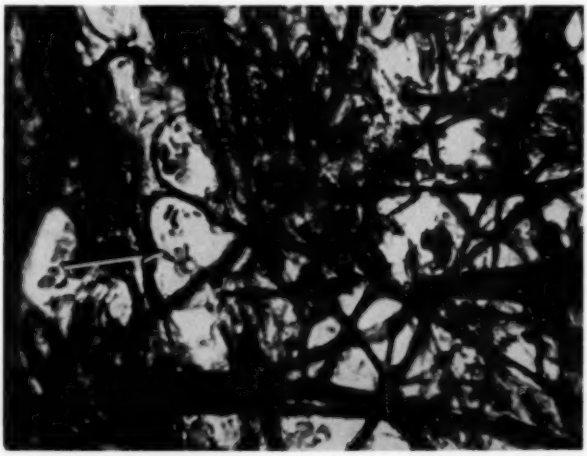

Fig. 40 (Wolter). Blood containing capillaries in the trabecular meshwork of a 50-year-old woman with hemorrhagic glaucoma. (Tangential section, Hortega stain, photomicrograph.)

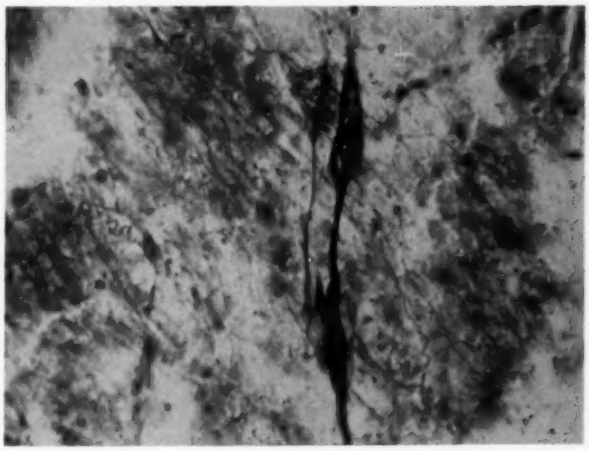

Fig. 41 (Wolter). Swollen nerve-fiber stump in the ciliary body next to the trabecular meshwork in the eye of a 77-year-old woman with absolute hemorrhagic glaucoma. Very delicate nerves supplying the muscle fibers of the ciliary muscle are seen all through the photograph. (Tangential section, Hortega stain, photomicrograph.)

relations of the trabecular changes to the degenerative changes in the ciliary muscle and in the ciliary processes but the limits of this talk do not allow to discuss these. You will have realized already that no evidence for an exiting new cause of the primary glaucomas has been found in this study. However, I hope to have confirmed some findings that have been seen with other staining methods and to have added a few points of interest and new views. It takes a lot of bricks to build a house and all I could do was to add a few bricks of knowledge to the eventual understanding of the pathology and cause of the glaucomas—which still seems to be far away.

SUMMARY

Tangential sectioning and silver staining were used to study the histopathology of the trabecular meshwork in glaucoma.

Sclerosis of the trabecular beams and pigment deposition were found as aging changes in normal trabeculae. Granularity of the collagen of the trabecular beams was seen as a nonspecific change in different types of pathologic involvement of the trabecular meshwork. However, granularity was not observed in normal trabeculae of eyes that were fixed immediately after enucleation. Eyes with advanced intraocular tumor were found to demonstrate pathologic alterations of the trabeculae.

The trabecular meshwork in cases of open-angle glaucoma was found to exhibit swelling and proliferation of the trabecular endothelium and chronic degenerative and reactive nerve-fiber changes in addition to changes that may be explained by normal aging. Granularity of the collagen can be found in the trabeculae in late stages of open-angle glaucoma and is considered a secondary change.

Only late stages were examined of the primary angle-closure glaucoma. These cases showed trabecular changes composed of atrophy of the trabecular endothelium and nerves and collapse of the trabeclular meshwork in addition to the changes that can be explained by aging. Granularity of the trabecular collagen may be found.

The trabecular meshwork of cases of secondary (hemorrhagic) glaucoma following occlusion of central retinal vessels was found to exhibit neovascularization and proliferation of trabecular endothelium. There was also accumulation of blood and other cells in the trabeculae. The changes of aging and granularity of the trabecular collagen as well as secondary angle-closure and collapse of the trabeculae were observed in all late stages.

University Hospital.

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Discussion

Dr. Bernard Becker (St. Louis, Missouri): You had two eyes with controlled chronic simple glaucoma and three eyes that were uncontrolled. Were there any differences in the histologic pictures in the two groups?

Another question: Is it possible that the finding of endothelial proliferation in hemorrhagic glaucoma might be related to the fact that the patients had underlying chronic simple glaucoma as the basis for their hemorrhage?

Dr. Wolter: All the photomicrographs of nerve changes of the trabeculae in open-angle glaucoma shown in this demonstration were taken from sections of the eyes of the patient who had well controlled glaucoma and good vision. I have seen similar nerve changes in the other cases of advanced open-angle glaucoma, but in these cases there were fewer remaining trabecular nerves and their pathology was more advanced.

My cases were extremes. Two eyes were of a patient with well controlled open-angle glaucoma who had no surgery. All other cases were late stages of open-angle glaucoma. These facts explain why I am not in a position to give a final answer to your question.

Dr. Becker: Did the controlled cases have this endothelial proliferation?

Dr. Wolter: Yes, all my cases of open-angle glaucoma had that.

Dr. Becker: To the same degree?

Dr. Wolter: I couldn't say for sure but they all had it to a definite degree. It is my impression that the late stages of open-angle glaucoma showed more cellular proliferation in the trabecular meshwork than the two eyes of the patient with relatively early and well controlled open-angle glaucoma.

The second question I cannot answer because I have not much more clinical information on most of the cases of secondary hemorrhagic glaucoma as I needed to be sure about the correct diagnosis. It has been only recently that I learned about your studies—as well as about the earlier findings of Sugar*—which indicate that hemorrhagic glaucoma often goes along with open-angle glaucoma in the other eye.

Dr. James H. Allen (New Orleans): I would

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* Sugar, H. S.: Arch. Ophth., **28**:587, 1942; Acta XVI Conc. Ophth. (Britannia) 1950, p. 846.

like to ask Dr. Wolter if he has had an opportunity to study the endothelial cells of the trabeculae or the questionable cells that contains these pigment granules in a large enough series of different ages to determine whether there is a greater amount of pigment in the older patients and less in the younger patients. That might throw some light on the question of whether these are cells are phagocytic or whether they are actually chromatophores.

DR. WOLTER: That is an extremely interesting question. It has interested me but I haven't had time to look into it.

In the first place, I think that a certain degree of pigmentation of the trabeculae is not always a pathologic finding. I have seen eyes without glaucoma and without other pathology that we knew of which exhibited very extensive pigment deposition in the trabeculae. On the other hand, I think that all cases of glaucoma that I have studied also showed pigmentation of the trabeculae.

THE INHIBITION OF CORNEAL VASCULARIZATION BY TRIETHYLENE THIOPHOSPHORAMIDE*

MAURICE E. LANGHAM, PH.D.
Baltimore, Maryland

A study has been made of the influence of triethylene thiophosphoramide (Thiotepa, Lederle Laboratories) on the rate of growth of new vessels into the cornea of the rabbit. In these experiments, vascularization of the cornea has been induced with alloxan using a technique described previously (Langham, 1952).

Triethylene thiophosphoramide (fig. 1) is an active antimitotic agent and is related chemically and pharmacologically to the nitrogen mustards in that it is a polyfunctional alkylating agent and is most effective on rapidly growing normal and neoplastic tissues. It has been shown to inhibit experimental tumours (Sparks, Walsh, Sebastianelli, Stevens, Lander, Halliday and Gleson, 1954) and has been used sucessfully to retard tumour growth in patients (Watson and Turner, 1959).

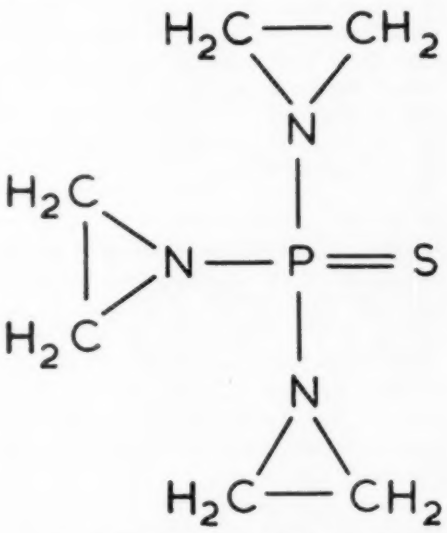

Fig. 1 (Langham). The chemical structure of triethylene thiophosphoramide.

METHODS

Adult rabbits (New Zealand white weighing 2.0 to 3.0 kg.) of both sexes were used in these studies. Vascularization of the cornea was induced with a solution of alloxan injected into the anterior chamber. One hundred mg. of alloxan was dissolved in 2.0 ml. physiologic saline and adjusted to pH 6.5 and the volume made up to 5.0 ml. A syringe containing 0.4 ml. of this solution was connected to the anterior chamber via a 27-gauge needle and the alloxan mixed with the aqueous humour by pushing the barrel of the syringe up and down several times. The needle was then pushed through the other side of the cornea and the syringe disconnected. The needle was withdrawn 15 minutes later. The corneal thickness was

* From the Wilmer Institute, Johns Hopkins University Medical School.

TABLE 1

THE EFFECT OF TRIETHYLENE THIOPHOSPHORAMIDE (TPA) ON NEW VESSEL GROWTH IN RABBIT CORNEA AFTER INJECTION OF ALLOXAN (DAY 1)

Series	7th Day	11th Day	17th Day
Control A	0.7±0.22 (6)	2.4±0.06 (6)	4.5±0.14 (6)
Controls B	1.8±0.25 (13)	3.2±0.15 (13)	5.7±0.3 (13)
Series I	—	2.7±0.23 (7)	3.1±0.29 (6)
Series II	—	3.1±0.29 (6)	3.3±0.31 (6)
Series III	1.6±0.20 (6)	1.9±0.26 (6)	—

The animals in Series I were injected intramuscularly with 2.5 mg./kg. of TPA daily from the 11th day; those in Series II were injected 2.5 mg./kg. of TPA subconjunctivally daily from the 11th day. Finally, the animals in Series III had one drop of an oil suspension of TPA (10 mg./ml.) instilled topically three times daily from the sixth day. Control series B are taken from Langham (1952). Results are expressed in mm. (Arithmetic mean ± standard error of mean.)

measured using an apparatus based on the method of Maurice and Giardini (1951). An aqueous solution of triethylene thiophosphoramide was made by dissolving 10 mg. in 1.0 ml. of physiologic saline. The composition of the suspension of triethylene thiophosphoramide in oil was as follows: Thiotepa 1.05 percent W/V, Tocopherols (34 percent in oil) 0.15 percent V/V and sesame oil made up to 100.

RESULTS

Table 1 and Figure 2 summarize the results of alloxan on the extent of vessel ingrowth into the cornea and also show the effect of triethylene thiophosphoramide (TPA) given intramuscularly, subconjunctivally and topically on the ingrowth of vessels: Typical changes in the experimental eyes of rabbits given TPA are shown in Figures 3, 4, 5, and 6.

The reaction of the cornea to alloxan in the control series was very similar to that found previously in a larger series of rabbits (Langham, 1952). The alloxan caused a rapid swelling of the cornea from an initial value of 0.4 mm. to approximately 1.0 mm. within 24 hours and the cornea remained swollen during the remaining period of the experiment. On the fourth to sixth days vessels started to grow into the cornea from the limbal region at a linear rate of approximately 400 μ per day.

In the two series of rabbits given intramuscular or subconjunctival injections of triethylene thiophosphoramide treatment was begun on the 11th day. At this period the mean extent of vessel ingrowth in the two series was not significantly different from the controls. Six days after intramuscular injections of TPA the mean extent of the vessel ingrowth was 3.1 ± 0.29 (6) mm.; similarly in those rabbits given subconjunctival injections for six days the mean extent of vessel ingrowth was 3.3 ± 0.31 (6) mm. These values are significantly below those in the control series ($p < 0.001$) and represent decreases of approximately 80 percent

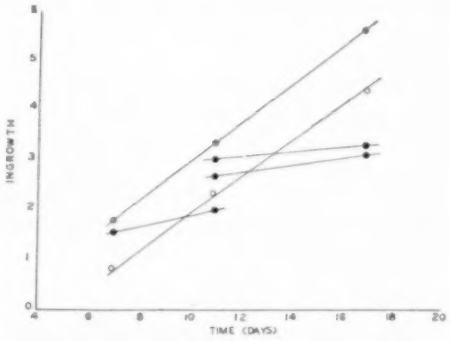

Fig. 2 (Langham). The mean extent of vessel ingrowth (mm.) in control (open circles) and treated (closed circles) eyes. The upper line connecting the open circles shows the mean ingrowth in 13 rabbits reported by Langham (1952). The lower open-circle line shows the mean of six experiments in the present study. The closed circles show the mean extent of vessel ingrowth in animals given triethylene thiophosphoramide intramuscularly (upper line), subconjunctivally (middle line), and by oil drops (lower line).

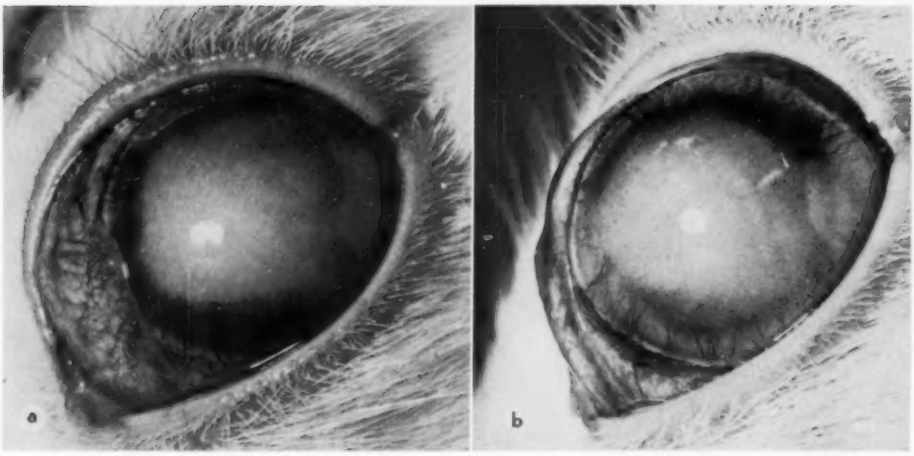

Fig. 3 (Langham). The effect of intramuscular triethylene thiophosphoramide (2.5 mg./kg. daily) on corneal vascularization. The initial injection of the inhibitor was given on the 11th day. (a) Cornea on 11th day and (b) 17th day.

in the rate of ingrowth. The corneal thickness of these eyes was found to remain greater than 1.0 mm. during the period these observations were taken.

In similar experiments the dosage was reduced to 0.5 mg./kg. of TPA given either intramuscularly or subconjunctivally daily. Under these conditions no inhibition of vessel growth was observed in the rabbits given the inhibitor intramuscularly and a variable effect in those injected subconjunctivally.

Although the intramuscular and subconjunctival injections of 2.0 mg./kg. of TPA daily caused an inhibition of new vessel growth, evidence of general toxicological reactions was observed. In the rabbits injected intramuscularly there was a significant loss in body weight. The change in the cellular composition of the blood of two of these animals before and after treatment with the inhibitor is shown in Table 2. Blood changes were also seen in those animals given subconjunctival injections of the inhibitor (2.0 mg./kg. daily) and the result of one pair of analyses is shown in Table 2.

In a final series of experiments one drop of an oil suspension of TPA (10 mg./ml.) was instilled into the eye three times daily from the sixth day after the alloxan injection and the results are recorded in Table 1 and Figure 2. In all rabbits the drops caused a significant reduction in the rate of ingrowth of vessels. The rabbits showed no loss in body weight and no change in blood composition. In three of these rabbits administration of triethylene thiophosphoramide was discontinued at the 15th day and it was found that new vessel growth recommenced (figs. 6 and 7).

Discussion

These experimental results show that new

TABLE 2

THE EFFECT OF TRIETHYLENE THIOPHOSPHORAMIDE ON THE HEMOGLOBIN AND WHITE CELL COUNT OF RABBIT BLOOD

Rabbits		Hemoglobin %	White Blood Cells (ml.$^{-1}$)
Controls		14.1 ± 0.64 (6)	6,670 ± 20.6 (6)
9107	Before	13.1	4,300
	After	3.7	800
9162	Before	16.4	6,500
	After	12.1	4,600
9081	Before	13.3	7,000
	After	11.5	4,700

Rabbits 9107 and 9162 were given 2.5 mg./kg. of TPA intramuscularly and 9081 2.5 mg./kg. of TPA subconjunctivally daily for eight days and the second analyses made on the 98th day.

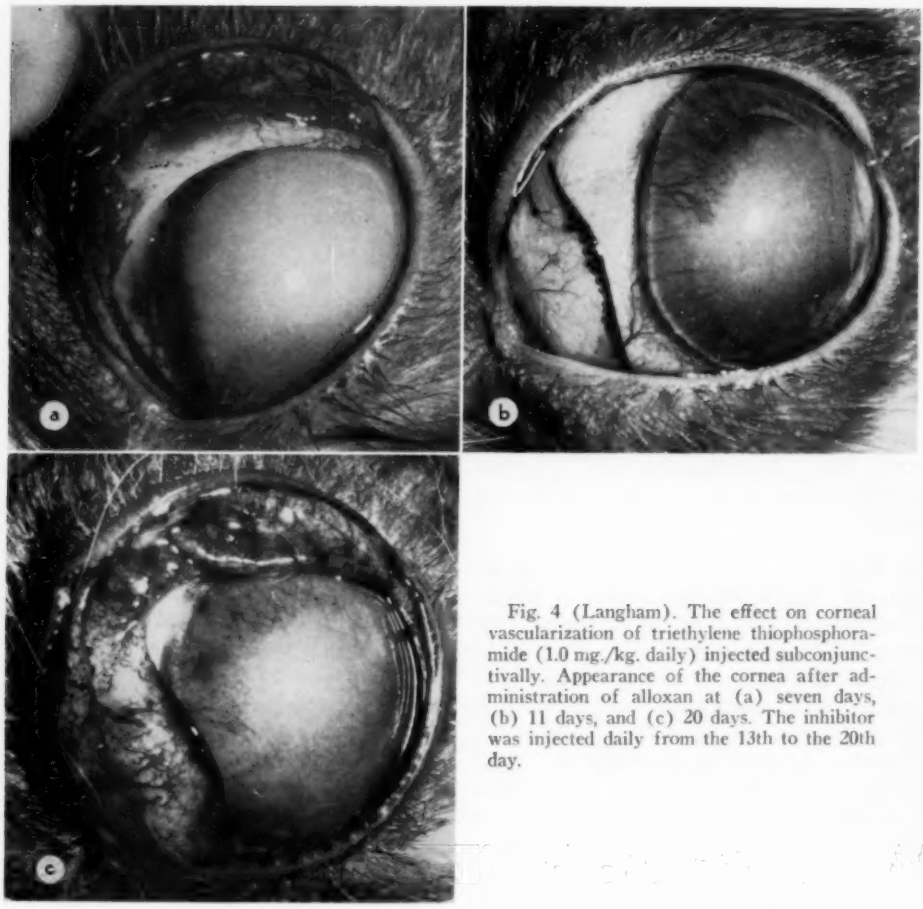

Fig. 4 (Langham). The effect on corneal vascularization of triethylene thiophosphoramide (1.0 mg./kg. daily) injected subconjunctivally. Appearance of the cornea after administration of alloxan at (a) seven days, (b) 11 days, and (c) 20 days. The inhibitor was injected daily from the 13th to the 20th day.

vessel growth into the oedematous cornea may be inhibited by triethylene thiophosphoramide given either systemically or applied directly on the eye. However, the results indicate that the cytotoxic properties of the compound limit its systemic application, for the dose needed to inhibit corneal vascularization also caused loss in body weight and marked haematologic changes. Similar toxicologic changes were observed after subconjunctival injections of the drug and this was almost certainly due to the rapid absorption of the highly soluble compound into the general circulation. It was for this reason that a suspension of the inhibitor in oil was prepared. Instillation of this on the eye proved effective in inhibiting new vessel growth and at the same time allowed the dosage to be reduced to a level below which cytotoxic changes were observed.

In view of the antimitotic character of TPA, there can be little doubt that the inhibition of new vessel growth was due to a suspension of capillary endothelial proliferation. It was therefore of particular interest that vessel growth recommenced on withdrawal of TPA for it means that the stimulus to new vessel growth persisted in the

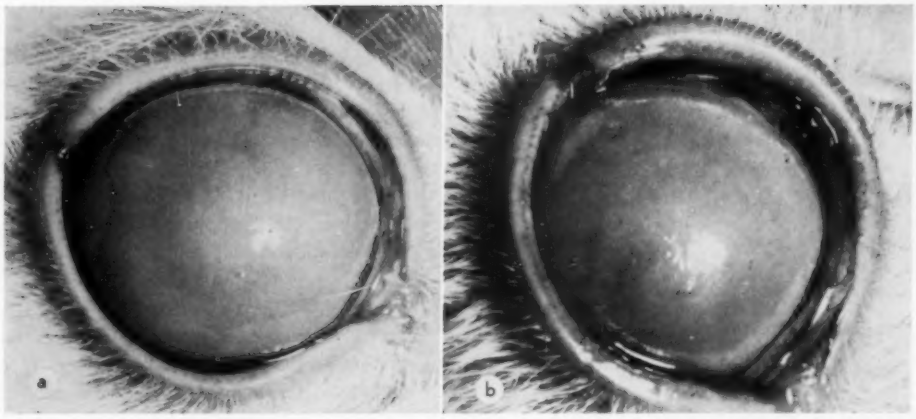

Fig. 5 (Langham). The influence of topical thiophosphoramide on corneal vascularization. Cornea after injection of alloxan (a) at six days and (b) at 15 days. From the sixth to the 15th day, one drop of the inhibitor suspension in oil was instilled three times daily. No ingrowth occurred over this period.

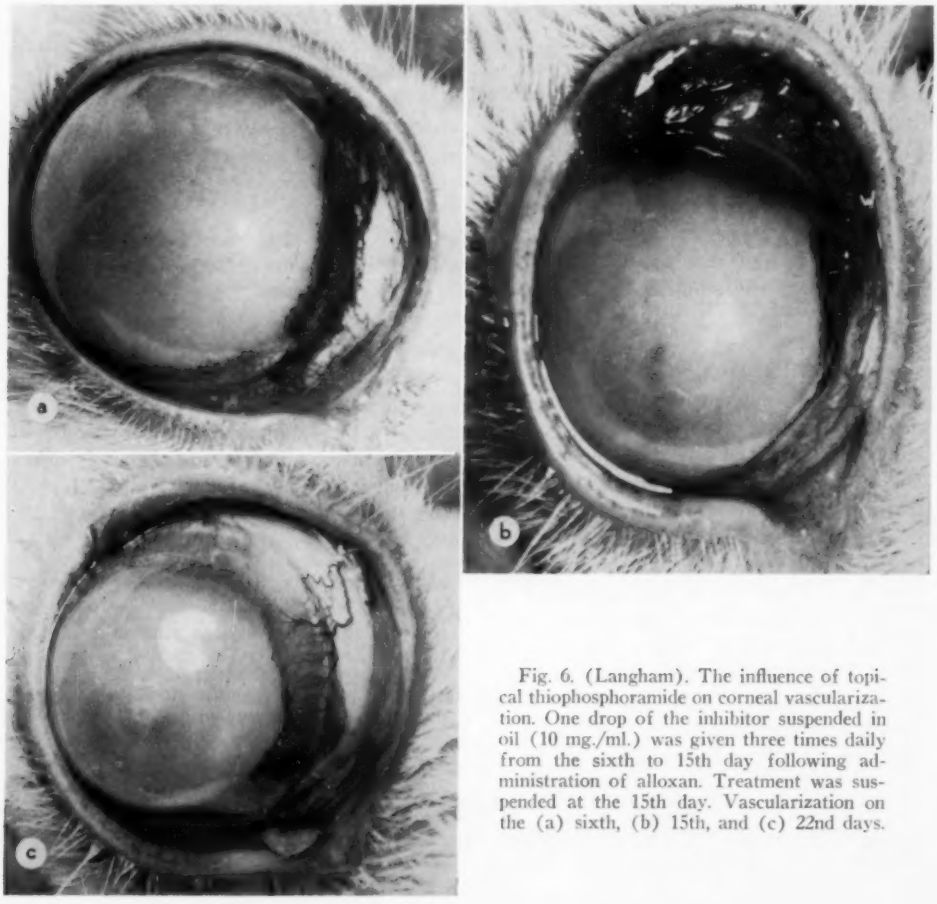

Fig. 6. (Langham). The influence of topical thiophosphoramide on corneal vascularization. One drop of the inhibitor suspended in oil (10 mg./ml.) was given three times daily from the sixth to 15th day following administration of alloxan. Treatment was suspended at the 15th day. Vascularization on the (a) sixth, (b) 15th, and (c) 22nd days.

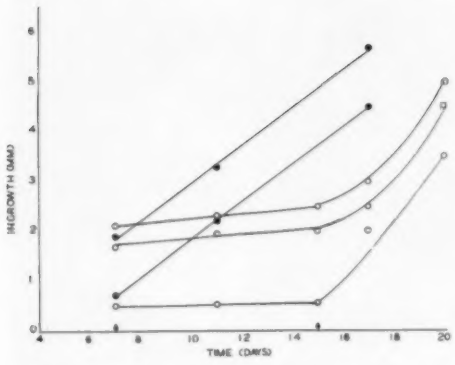

Fig. 7 (Langham). Effect on corneal vascularization of triethylene thiophosphoramide (10 mg./ml. suspension in oil) administered topically daily from the seventh to the 15th day (open circles). The closed circles represent the mean extent of vascularization in the control series.

cornea for many days after injection of alloxan. This is readily explained on the basis of the concept put forward by Cogan (1949) that corneal oedema in the limbal region is the stimulus to neovasculogenesis, for the cornea remained grossly swollen during these experiments. At the same time, the results do not rule out the alternative possibility that the stimulus to neovasculogenesis is organic in nature (Langham, 1953).

It is well known that cortisone can inhibit new vessel growth in certain conditions and the present studies throw further light on the mode of action of this hormone. Duke-Elder and Ashton (1951) suggested that cortisone inhibits corneal vascularization by a direct suppression of endothelial proliferation, and indirect support for this view was found from the significant decrease in the renewal of corneal endothelium in cortisone treated rabbits (Ashton and Cook, 1951). On the other hand, in a previous investigation (Langham, 1952) it was shown that cortisone would not inhibit the ingrowth of vessels into the swollen cornea but would decrease the swelling that precedes new vessel growth. Under these conditions, the compactness of the tissue could prevent new vessels entering the cornea. This interpretation is now strongly supported by the present observations that TPA, a mitotic inhibitor, suppressed vessel growth in the swollen cornea.

Summary

1. The influence of a mitotic inhibitor triethylene thiophosphoramide on the rate of growth of new vessels into the cornea of the rabbit has been studied. Vascularization was induced with alloxan injected into the anterior chamber.

2. The inhibitor was found to cause a decrease of over 80 percent in the rate of ingrowth of new vessels when given intramuscularly, subconjunctivally or topically.

3. The inhibition of vessel growth occurred in the presence of a grossly thickened cornea and it was found that new vessel growth recommenced on withdrawal of the inhibitor.

4. Cytotoxic changes in the blood of animals given intramuscular or subconjunctival injections of the inhibitor were found, but none in the series of animals treated topically.

5. It is concluded that triethylene thiophosphoramide may be used to directly inhibit capillary endothelial proliferation in the oedematous cornea and that it is effective when instilled into the subconjunctival sac.

The Johns Hopkins Hospital (5).

Acknowledgments

I wish to express sincere appreciation to Sir Stewart Duke-Elder for his interest in this study and to thank the Medical Research Council, England, for defraying the cost of this study. I am also indebted to Lederle Laboratories for donating the triethylene thiophosphoramide used in this study.

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Discussion

Dr. Winston Roberts (Winston-Salem, North Carolina): Dr. Langham, what strength is the oil supension that you used, and where are you getting it?

Dr. Langham: Thiotepa is made by Lederle, and we have been using a suspension of 10 mg./ml.

Dr. Hunter Romaine (New York): Dr. Langham, how long can you continue this? What is the longest period of time you have kept it in continuation?

Dr. Langham: About two to three weeks.

Dr. Romaine: Does vessel growth continue after that time?

Dr. Langham: Yes, provided the cornea is still thick.

Dr. Grant: I am interested to know what effect the compound had on normal rabbit eyes when applied in the same amount for the same period of time.

Dr. Langham: I have applied drops of Thiotepa three times daily on normal eyes for a period of two weeks and found that there was no change in the thickness of the cornea.

Chairman Romaine: Do you have sections on these eyes?

Dr. Langham: No.

Dr. James E. McDonald (Chicago): I wonder what these eyes might look like a year later. It seems that you are getting a local radiomimetic effect.

In our work with beta radiation we found that although there might be no superficial evidence of damage, if there were a therapeutic effect with beta radiation, a year or two later we would get a growth of telangiectatic blood vessels. They didn't seem to be aggressive looking, but they did cause a cosmetic deformity in some of our beta radiation patients.

As far as I know, local radiomimetics have not been studied from the standpoint of their possibility of producing a subsequent telangiectasia.

VARIOUS LABORATORY ASPECTS OF ALPHA CHYMOTRYPSIN*

Charles W. Damaskus
Kankakee, Illinois

The use of alpha chymotrypsin in cataract surgery was a significant milestone in the clinical uses of enzymes. When I speculate on the future I visualize that comparable advances are imminent.

Realizing that considerable data has been published in your journals on the techniques involving the use of alpha chymotrypsin in cataract surgery, I choose to discuss another area which I hope you will find informative. Briefly, I intend to describe how alpha chymotrypsin is prepared, characterized and standardized; the present stability data and compatibilities of alpha chymotrypsin with some of the drugs used in cataract surgery.

Alpha chymotrypsin is extracted and purified from bovine pancreas using an

* From the Research and Development Department, Armour Pharmaceutical Company. Presented at the Midwinter National Meeting of the Association for Research in Ophthalmology, Inc., December 4, 1959, Medical College of Georgia, Augusta, Georgia.

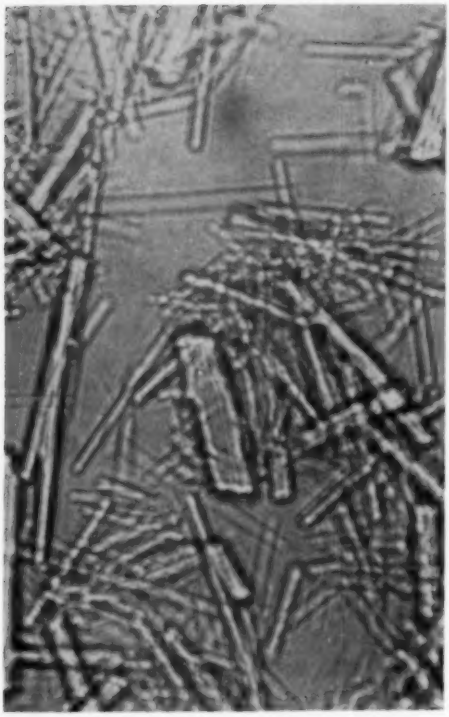

Fig. 1 (Damaskus). Chymotrypsinogen crystals.

Armour modification of the conventional published technique. Basically, the process involves grinding the frozen pancreas glands and extracting the powder with a concentrated phosphoric acid alcohol solution. The residue from the previous extraction is suspended as a slurry and ammonium sulfate added. After centrifugation the residue is discarded. The supernatant containing the zymogen is precipitated with ammonium sulfate. The precipitate contains the chymotrypsinogen and the filtrate after subsequent fractionations yields trypsinogen, the precursor of trypsin. The chymotrypsinogen is then solubilized in water, and a low concentration of trypsin added as the activator. The activation is allowed to proceed. The alpha chymotrypsin is precipitated from the activated solution with ammonium sulfate, dialyzed against distilled water and lyophilized as a bulk powder. The bulk alpha chymotrypsin is assayed for activity, moisture, ash and total protein. The alpha chymotrypsin is then solubilized in PF distilled water, sterilized by filtration, aseptically filled into vials, frozen, lyophilized, sealed under dry nitrogen and assayed again (figs. 1, 2, 3, and 4).

Each mg. of alpha chymotrypsin contains 1100 to 1200 Armour units of proteolytic activity and is virtually salt free. The proteolytic activity is determined by a modification of Anson's hemoglobin method in which one unit of activity is that amount which, upon incubation with the hemoglobin substrate (urea denatured bovine hemoglobin) will release substances that, when reacted with Folin-Ciocalteau phenol reagent, will result in the formation of a colored solution of equal intensity to that produced from the reaction of 5.52×10^{-6} millimoles of tyrosine. In the interpretation of assay results, a maximum error of $\pm$ 8.0 percent should be used.

I previously stated that each mg. of alpha chymotrypsin contains 1100 to 1200 A.U./mg. Thus, when packaged, vials contain

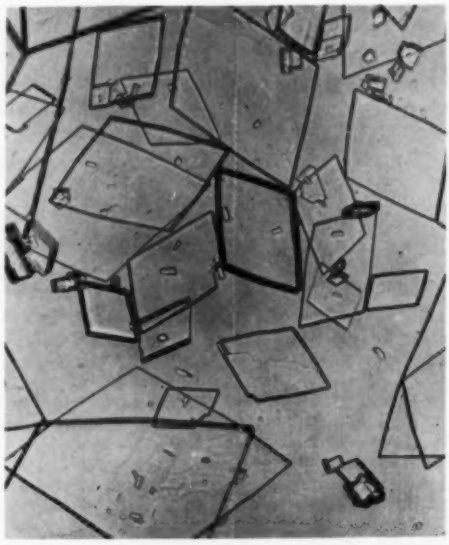

Fig. 2 (Damaskus). Alpha chymotrypsin crystals.

Fig. 3 (Damaskus). Chymotrypsinogen electrophoric pattern.

550 to 800 μg. of chymotrypsin solids and are labeled as 750 A.U./vial.

Our laboratory assayed different alpha chymotrypsin powders and obtained assay values of 750 A.U./mg. to 1300 A.U./mg. On this basis, we urged that the clinical evaluations be conducted on a unitage basis instead of a dilution of solids to volume. I believe that all the commercial alpha chymotrypsin preparations available in the United States are now labeled on a unitage basis, using the previously described substrate assay.

The question in reference to the stability of alpha chymotrypsin after reconstitution with normal saline occasionally arises. The following data are considered characteristic. Sterile lyophilized alpha chymotrypsin in vials containing 700 A.U. of activity were reconstituted, each with 5 ml. of sterile normal saline and assayed initially and after 24, 48 and 72 hours storage. The following assay results were obtained in A.U. per ml. (table 1).

Stability of reconstituted alpha chymotrypsin

Vials do not contain a preservative and, thus, are considered single dose containers and should be discarded immediately after use. When the alpha chymotrypsin solution is used within 8 hours after reconstitution

Fig. 4 (Damaskus). Chymotrypsin electrophoric pattern.

TABLE 1

STABILITY OF RECONSTITUTED ALPHA CHYMOTRYPSIN

Time (hr.)	Proteolytic Activity (A.U./ml.)
Initial	140
24	122
48	104
72	116

there is no loss in activity.

Compatibility of alpha chymotrypsin with drugs used in the eye is another question that has arisen on several occasions. The following assay data was obtained from samples that were added to normal saline reconstituted vials of alpha chymotrypsin (table 2).

COMPATIBILITY OF ALPHA CHYMOTRYPSIN WITH VARIOUS COMPOUNDS

These data indicate that epinephrine at a concentration of 10 mg./ml. or 1:100 dilution will effectively inactivate chymotrypsin.

The last item I would like to mention in this discussion is the subject of chymotrypsin inhibitors. To demonstrate the action of chymotrypsin inhibitors, the following experiment was designed. Rabbit blood was withdrawn and centrifuged. The serum was aspirated and pooled. To one sample of rabbit serum 5500 A.U./ml. of crystalline trypsin was added, and to the second sample 5750 A.U./ml. of crystalline alpha chymotrypsin was added. Samples were retained at room temperature and assayed at various time intervals. The following results were obtained (table 3).

TABLE 3

INHIBITOR EFFECT

Initial	Trypsin Proteolytic Activity 46 A.U./ml.	Chymotrypsin Proteolytic Activity 485 A.U./ml.
		(A.U./ml.)
15 min.	Nil.	500
1 hr.	Nil.	510
2 hr.	Nil.	500
3 hr.	Nil.	505
3.5 hr.	Nil.	465

INHIBITOR EFFECT

These data indicate that rabbit serum contains sufficient trypsin inhibitor to bind approximately 99 percent of the trypsin activity and sufficient chymotrypsin inhibitor to combine with approximately 90 percent of the chymotrypsin activity. When proteolytic activity is directly associated with a substrate effect, such as alpha chymotrypsin on the zonule, the concentration of inhibitor in the residual fluids is a factor to consider. It is conceivable that variation in inhibitor concentration may exist in different conditions and individuals. I would like to pose the question, "Is this the reason diffi-

TABLE 2

COMPATIBILITY OF ALPHA CHYMOTRYPSIN WITH VARIOUS COMPOUNDS

Drug	Concentration (mg./ml.)	Estimated Initial (A.U./ml.)	Proteolytic Activity After R. T. Storage (A.U./ml.)
Pilocarpine HCl	1 (0.1%, 1:1,000)	160	167 (1 hr.)
Pilocarpine HNO_3	1 (0.1%, 1:1,000)	160	166 (1 hr.)
Pontocaine HCl	5 (0.5%, 1: 500)	153	150 (1 hr.)
L-Arterenal bitartrate	10 (1.0%, 1: 100)	153	144 (1 hr.)
L-Arterenal bitartrate	1 (0.1%, 1:1,000)	153	213 (1 hr.)
Epinephrine	10 (1.0%, 1: 100)	143	Nil. (1 hr.)
Epinephrine	1 (0.1%, 1:1,000)	153	184 (1 hr.)
Acetyl choline	0.4 (0.04%, 1:2,250)	134	102 (24 hr.)
Additional Compounds Tested			
Cystine	50	130	130 (4 hr.)
Urea	50	120	120 (4 hr.)
Boric acid	22	135	135 (4 hr.)
Sodium bicarbonate	20	135	125 (4 hr.)
Hydrogen peroxide	1	145	Nil. (4 hr.)

culties are involved in some of the problem extractions?" The variation in inhibitor concentration in systemic circulation is now being investigated in various organic conditions.

The use of a chymotrypsin inhibitor becomes practical in irrigating the anterior and posterior chambers of the eye after lens removal. With this technique there would be complete assurance of no latent chymotrypsin effects on the iris, cornea and other tissues involved.

SUMMARY

Alpha chymotrypsin preparation, characterization and stability were discussed. Data were also presented in reference to chymotrypsin compatibility with medicinals used in the cataract surgical technique. It was suggested that if serum or blood is present in the anterior or posterior chamber during cataract surgery, chymotrypsin inhibitors may selectively bind alpha chymotrypsin and interfere with zonulolysis.

BINOCULAR SUMMATION OF SUBLIMINAL REPETITIVE VISUAL STIMULATION*

ROBERT H. PECKHAM, PH.D., AND WILLIAM M. HART, M.D.
Bethesda, Maryland

In order to describe our experimental results it is necessary to review the basic method of determining limens or thresholds, which has been established by psychologists working in the field of physiologic optics.

When a visual stimulus is very weak, it cannot be seen. When such a stimulus is very strong, it is always seen. Between these extremes there exist stimulus values that are only rarely seen, or are nearly always seen. Thus the threshold is not truly a sudden change, but a gradual one. For convenience, we can describe the threshold as the stimulus value that is seen half the time, and not seen half the time, in a large number of trials. This is called the 50-percent probability of seeing threshold.[1] Stimulus values weaker than this can be called subliminal values, because they will be seen with decreasing frequency, always less than half the time.

This phenomenon of stimulus-response relationship is found in all sense modalities, as well as in vision. It is a phenomenon of the response to the intensity of sound, to the effectiveness of weight through the proprioceptive system, to taste and to smell. No measurement of the limit of perception is statistically meaningful unless its relationship to the probability of response is known.

There are many thresholds in vision. There is the threshold of least light to a dark-adapted eye, the threshold of difference of color, in hue or saturation, and the threshold of change in brightness, often called the contrast threshold. This contrast threshold is of greatest interest to us because it includes the concept of adaptation of the photoreceptive system to the general ambient luminance. In studying contrast one asks, what is the least perceptible change in brightness; either higher or lower, than the background? The contrast threshold exhibits the probability curve, and therefore permits the measurement of probability of seeing.

The specific contrast thresholds we have measured refer to repetitive stimuli. Instead of measuring the probability of seeing for various contrasts, we have measured the probability of seeing for various uniformly repeated exposure times at a constant low contrast. The stimulus is alternated above and below the apparent brightness of the background at five-percent contrast each way. The rate of alternation, of which each

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* From the Eye Research Foundation of Bethesda. This work was supported by Contract Nonr 2750(00) with the Office of Naval Research.

phase is equal in time, is converted to milliseconds of on-time (which equals milliseconds of off-time). In the threshold range, the subjective response to this type of repetitive stimulus is a perception of irregular spotty flashes, apparently of quite random nature, which closely resemble the visual appearance of the scintillation of a phosphorescent crystal in a radiation field. This response is one of the series of perceptual phenomena associated with repetitive or intermittent visual stimuli and known as "flicker."[2]

Our procedure also includes one other very important experimental control, which must be included in presentation. The times of the stimuli vary in a predetermined random order. Thus the alternating stimulus is presented at a frequency of 20 per second, for example, for about 10 seconds, then at 27 per second, then at 23, then at 35, and so forth. This is to require that each succeeding rate be unknown to the subject, so that his response is determined by the stimulus rate, rather than by any anticipation on his part. This procedure tends to eliminate subject bias, and also serves as a good check of both malingering and insight by the subject examined.

In our procedure the background adaptation and pupil size are maintained by a large white field at 50 cd/m^2 luminance, over 60 degrees in subtense. In the center of this field, a 2.0-cm. spot, viewed at 100 cm., contains the alternating stimulus of nearly equal brightness. This spot is 1.15 degrees in subtense, or well within the foveal area.[3] The stimuli are selected by the successive positions of an 11-pole switch, wired in the desired random order, and are presented for about 10 seconds at each position clockwise and counter-clockwise, for three complete cycles. This presents 10 selected frequencies six times and the 11th three times, for each set. Whenever the subject perceives the scintillation, he responds by sounding a buzzer.

Seventy-eight subjects aged 16 to 60 years, were studied but for reasons described below, only the records of 60 subjects were used. All of the subjects had normal binocular vision with acuity 20/20 or better in each eye after refractive correction, which was worn if prescribed. The right, the left, and both eyes were measured. The two monocular measurements were made using a translucent occluder, which prevented form perception, but maintained adaptation level. Each subject was given 63 measured stimuli, each three times, therefore 11,340 trials are analyzed in the present report.

The results of the analysis of these data are shown in Figure 1. The raw data are first rearranged in serial order, against the time in milliseconds of half cycle. At the right of the figure, at 22 milliseconds, all stimuli are always seen for either and both eyes. The response of the right eye alone is indicated as p_R, that for the left eye as p_L, and that for both eyes as p_B. The response for the two eyes together is superior to either eye alone. This is shown by the shift of the p_B curve to the left, which indicates that at a given stimulus level, say 17 milliseconds, the probability of seeing binocularly exceeds the probability of seeing monocularly.

Now, it should be possible to compute the binocular response, knowing the two monocular responses.[4] The subject cannot know, when both eyes are working together, if he sees with the right eye, the left eye, or both eyes. This is analogous to the measurement of probability of seeing with one eye in each of two heads. Imagine two subjects watching the spot simultaneously, each with only one eye. If either or both report seeing, it is credited as response. Only if both fail to see do we credit failure of response. Such an effect could be predicted from the known behavior of these two monocular subjects. Thus if, at a certain stimulus level, one of them responds with 40 percent probability of the time, he fails with 60 percent probability. Imagine the other responds with 60

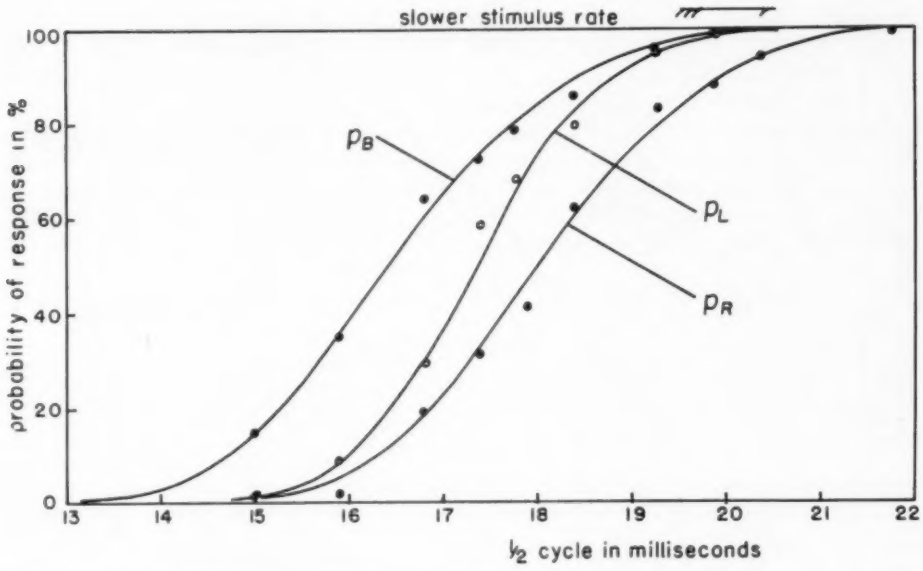

Fig. 1 (Peckham and Hart). Frequency of seeing curves for right eye (p_R), left eye (p_L) and both eyes (p_B), analyzed from data on 11,340 trials with 60 subjects.

percent probability, which is 40 percent improbability. Their average is indeed 50 percent, but their conjoint responses must be measured, not by the average, but by the computed improbability that both fail simultaneously. This is predicted by the product of the separate improbabilities, that is, the product of 0.60×0.40. This yields the value 0.24, which is the chance or probability that both will fail at once. The chance of either or both seeing, which is the chance of a credited response, is $1.00-0.24$, which equals 0.76. Thus when either or both respond, the probability of response is greater than the average of individual responses.

Similarly, a subject with both eyes open has four conditions of seeing, he sees with the right eye only, he sees with the left eye only, he sees with both eyes, or he fails to see with either and both eyes, for the specific stimulus. This analysis, derived for a single and discrete stimulus, applies to repetitive stimuli also, although it is to some extent dependent upon the period of stimulation, which controls the number of repetitions. The effect of the repetition, in the experimental situation, is to spread the probabilities over a wider stimulus range, that is, to increase the value of the standard deviation of the response distribution. This is indeed a great advantage, since, first, it permits a more reliable estimate of individual differences, and second, it more closely resembles uninhibited natural seeing, when the uncontrolled stimulus becomes repetitive because of the continual saccadic eye movements.

Consequently, since we have recorded complete probability curves for each single eye of our subjects, we should be able to compute their binocular responses. In making this computation, only those records that show intermediate distributions can be used. Thus, if a set of records for a subject shows either complete responses to all stimulus levels, or no response to any stimulus level, for right, left, or both eyes, none of his records can be used for this type of computation. Of the 78 subjects measured, 60 records permitted the computations.

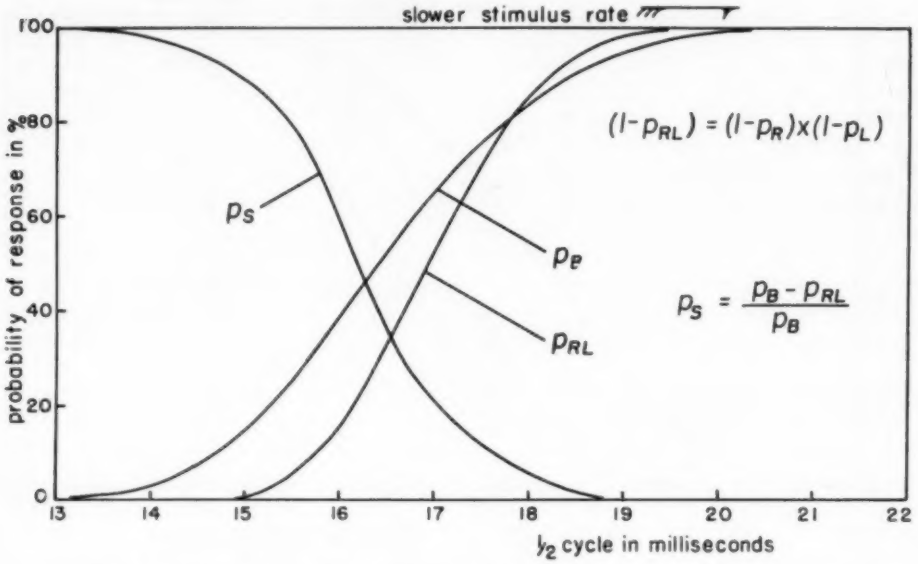

Fig. 2 (Peckham and Hart). Predicted frequency of seeing from two monocular records (p_{RL}) compared to empirical binocular responses (p_B), according to the formula shown. The curve of binocular facilitation (p_S) indicates that this effect depends mostly upon subliminal stimuli.

Figure 2 shows the results of such a computation. The curve p_{RL} indicates the computed trace of binocular prediction, according to the improbability products of the formula shown. The actual binocular response, however, is greater than this prediction. The experimentally determined curve, "p_B", exceeds the responses shown in the predicted curve "p_{RL}." Consequently we are forced to conclude that the binocular response includes some kind of facilitation over the two monocular responses. Statistically, the two curves, p_B and p_{RL}, can be shown to be mutually independent, although the overlapping section at the shoulder of the curves is statically insignificant.

Since there is such a difference, which we describe as binocular facilitation, the curve p_S has been devised to graphically express the difference, as a relative contrast in probability of response, by the formula shown in figure two. The facilitation exists mainly in the area below the 50% probability of response, that is in this sense, it is subliminal. What responses are found in the toe of the experimental binocular curve, p_B, are indicated in the differential distribution curve, p_S, as almost entirely related to the dinocular facilitation.

Now, it seems obvious, failing efferent fibers to the retina in the optic nerve, that the facilitation site must lie beyond the optic chiasma. Schrier and Sperry have found evidence of a subcortical integrating system in "split-brain" cats, evidenced in certain visuo-motor functions.[5] Bishop has reported interocular synapses within the lateral geniculates.[6] There is a need for specific electroneural recording of responses, monocular and binocular, as described by Talbot and Marshal.[7] If possible, these responses should be traced from the retina, directly or as corneal potentials, from both the optic nerves and the optic tracts, from the area of the geniculates, from within the optic radiation, and from the visual cortex, first in animals, and later, possibly in man, coincident with operative procedure, as has Penfield.[8]

It is the opinion of the authors that the use of repetitive stimuli lends itself admirably to this purpose. Hech and Getterström have shown that the usual masking effect of noise over signal, at the occipital lobes, can be overcome by the summation of such repetitive stimuli, in tracing a sinusoidal retinal stimulation at low sonic frequencies.[9] The phenomenologic observation of the scintillating appearance of a critically flickering light leads to the conjecture that a counting rate procedure may be superior to attempts at tracing the entire electroneural response at the various recording sites mentioned above. Finally, the flicker phenomenon itself is a discrete response, to which conditioned reflexes can be associated, in both animals and man after the manner of Hilgard, in order to relate electroneural traces to perceptual responses.[10]

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Discussion

Dr. Alpern: I followed the various researches of Drs. Peckham and Hart with considerable interest, and I want to congratulate them on their interesting work.

As I remember the apparatus, Dr. Peckham, one makes no attempt to control variations in pupil size in making these measurements. It occurs to me that the size of the pupil is different when either eye is fixing than when both eyes are fixing; and when the size of the pupil varies, the retinal illuminance must vary.

I wonder to what extent this influences the differences between measurements on either eye and measurements on both eyes together.

Dr. Peckham: It is a very obvious question, and one we have not failed to consider. The pupil size is well controlled by the very large field. There are no changes in the course of an experiment in the overall illumination to the eye. The brightness of the flickering spot varies by a very small amount, at that level of illumination, increasing only five percent or decreasing five percent below that level; so there is no significant change in brightness throughout the experiment.

The effect of the occluder is not to decrease the illumination but to make it impossible for the occluded eye to see anything clearly. It is a frosted material so that the light continues.

The results are accumulated for a large number of patients, so that individual differences in pupil size and consequently individual differences in retinal illumination are constant and added throughout. In effect they are averaged in. So, they would not have an effect on the results. The only effect would be in the difference between the binocular and the monocular records.

Your point would be that under some conditions there may have been more light binocularly than to either monocular level. The answer to this is that the occluded eye is not involved in the perception of the flicker. The light is the same for either occluded eye and for both eyes binocularly.

Since the occluder does not decrease the illuminance, there is no reason to think the occluder will increase the pupil size. It is a fairly high level field. Fifty candles per square meter is a bright room illumination. Under these circumstances, then, we feel that what we have shown here is an increase in the probability of seeing that has resulted from the use of the two eyes instead of one, which we call

binocular facilitation.

Finally, the change in the Limen: You will recall from the slide that the slope was changed. The 50-percent level shift is not very great, and is not as great as we would expect even with a modest change in brightness.

DR. ALPERN: Just to be certain of this point, it might be well to make some measurements of the pupil size under stimulus conditions, first without the occluder and then with it.

DR. PECKHAM: Yes, and we are planning to do that for other purposes.

DR. ALPERN: I suppose this is really not the place to get into a methodological discussion of the various methods of making flicker measurements, but I can't resist the temptation to tell you of some work that is going on in our laboratory in collaboration with Mr. Sugiyama, one of my graduate students, because it reflects some questions on the validity of using the constant stimulus method in the way you are doing it. Let me just tell you what we have been finding.

Mr. Sugiyama and I have been looking at flickering lights and measuring the effect of looking at a pulsing light on measurements of CFF. What we have found (and this has also been described by others) is that if one looks at a light which is pulsing below the CFF, the measurement of CFF goes down as a consequence of looking at this pulsing light.

This kind of result, I think, was beautifully demonstrated by Dr. Hart and you in a paper which you published a few weeks ago, in which you found that if you made your psychophysical procedure at what you called a slow rate and a fast rate, you got a different kind of flicker contour. Your curves were shifted over.

I think this is a clear demonstration of the same effect. I wonder if you have any comments on that.

DR. PECKHAM: I might say that the effect we found was monocular. I did not report in this binocular paper that we also found a confirmation of the same effect in the measurements made the second time around in the two monocular measurements. Again there was a distortion of the form of the psychophysical curve that is a function of the rapidity of the stimulus, and we have interpreted this (whether we are right or not) as a kind of monocular and retinal phenomenon occurring (if it does occur) within the retina itself, in the nuclear layer of the retina, whereas the binocular effect is quite outside the retina, unless you try to imagine some kind of fibers going back in—and nobody has found them.

However, as far as pupil size is concerned, I would like to make one more point. We have been making studies in shifting the level of illumination sharply, and here we have found that pupillary size is a control, and so we are making photographic measurements of the pupillary size.

We had a reason for not using an artificial pupil. All of our measurements, we found, after some effort, are most easily made when the field is quite open and free to the subject. Our interest originally in making these measurements was to determine the sensitivity of the subject to the entire retinal image. We felt that an artificial pupil to some extent would vitiate the value of these measurements.

So, we have tried to control the pupil size by the general illumination. When you do change the luminance you get a change in pupil size.

THE EFFECT OF HYPOTHERMIA ON AQUEOUS HUMOR DYNAMICS*

I. INTRAOCULAR PRESSURE AND OUTFLOW FACILITY OF THE RABBIT EYE

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INTRODUCTION

Although the use of cold water immersion for its sedative effect has been known for many centuries, the term hypothermia was not introduced until 1941.[1] Widespread interest in the physiological and biochemical effects of hypothermia in man and animal have followed the suggestion that such a technique might permit surgeons to operate in a bloodless field.[2] With falling body temperature oxygen consumption of the tissues decreases[3] and many physiological functions decrease in rate. There appears to be a general depression of the cardiovascular, renal, and central nervous systems by cold.

Little has been reported about the effect of hypothermia on the eye. With fall in body temperature, the pupils become large and fixed. Reversible changes occur in the cornea

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and the lens with extreme cooling to temperatures near and below freezing.[4-6] In the present studies a profound effect of hypothermia on aqueous secretion has been observed.

Methods

Male albino or California rabbits from Haskins Rabbitry, Saint Louis, weighing 2.0 to 3.0 kg. were used throughout this study. Each rabbit was anesthetized, initially, with thiamylal sodium,† 0.5 cc./kg. by parenteral administration followed by booster doses of 0.5 cc. as required during the induction period. No further injections were required once the rectal temperature fell below 30°C. and cold narcosis could take over.

Immediately following parenteral anesthesia, the rectal temperature was taken and the intraocular pressure was measured using the Schiøtz tonometer. A laboratory thermometer, inserted 13 to 15 cm., was used for all rectal temperature determinations. The animal was at once immersed into an ice water bath (fig. 1) maintained at 1°C. to 2°C. Room temperature was maintained at approximately 20°C. The Schiøtz scale readings and concomitant rectal temperatures were recorded at intervals throughout the experimental period. After removal from the bath, the rectal temperature generally fell 2°C. to 3°C. further.

Tonography was performed with an electric tonometer.[7] Tracings were made on a Leeds and Northrup recorder. Topical tetracaine (0.5 percent) was used for those rabbits studied at normal temperatures; however, it was not required for those animals studied under hypothermia. Flow rates were calculated from the equation $F = C\ (P_o - P_v)$ assuming an episcleral venous pressure of 9.0 mm. Hg. Schiøtz scale readings were interpreted according to Wistrand's calibration curve for the rabbit.[8]

Perfusion in vitro and in vivo was performed by methods already described.[9,10] The facility of outflow in the living rabbit eye was determined by the equation: $C = I/P_I - P_o$, where

I = rate of saline inflow (µl/min.)
P_I = inflow pressure (mm. Hg)
P_o = intraocular pressure before cannulation (mm. Hg)

Perfusion in the dead rabbit was performed in the same manner as in the living and the facility of outflow was determined by the equation $C = I/P_I$.[11]

Results

Mean values of Schiøtz readings and the

† The thiamylal sodium (Surital sodium) used in this study was provided by Parke Davis.

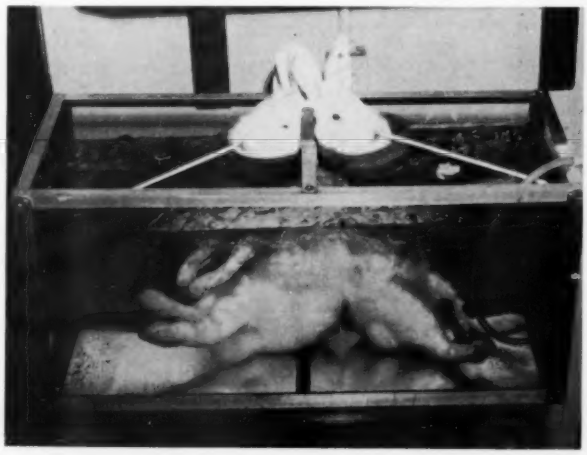

Fig. 1 (Pollack, Becker and Constant). Ice water immersion of rabbits. Oral temperature offers estimate of the rectal temperature. Cork collar adds protection against drowning.

TABLE 1

SUMMARY OF TONOMETRIC (SCHIØTZ) DETERMINATIONS OF INTRAOCULAR PRESSURE

Temperature °C.	No. Eyes	Scale Units*	Intraocular Pressure* (mm.Hg)	p (vs. 39.5°C.)
39.5	35	3.3±1.3	21.0±3.0	
35.5	12	3.5±1.3	20.5±2.5	0.7
33.0	29	4.1±1.6	19.0±3.2	0.05
29.5	34	5.6±2.1	16.5±3.1	<0.001
27.0	11	7.2±2.8	15.0±3.5	<0.001
26.0	19	7.5±2.0	14.5±2.4	<0.001
24.0	27	8.3±3.0	13.6±3.1	<0.001
22.0	18	8.7±2.4	13.0±2.3	<0.001
18.5	23	10.9±3.5	11.5±2.9	<0.001

* Mean ± S.D.

corresponding intraocular pressures obtained before and during the progress of hypothermia are summarized in Table 1 and Figure 2. Data thus obtained within 1.5°C. of the tabulated temperatures were averaged for analysis. Intraocular pressure decreased from a normothermic average of 21 mm. Hg to 11.5 mm. Hg at 20.0°C. When plotted as a logarithmic function, the intraocular pressure fell exponentially with the decline in rectal temperature (fig. 3). There was a 50% decrease in pressure for every 20.5°C. fall in temperature. By extrapolation, the intraocular pressure approaches episcleral venous pressure at about 15°C. This process shows a temperature coefficient, Q_{10}, of 1.4.

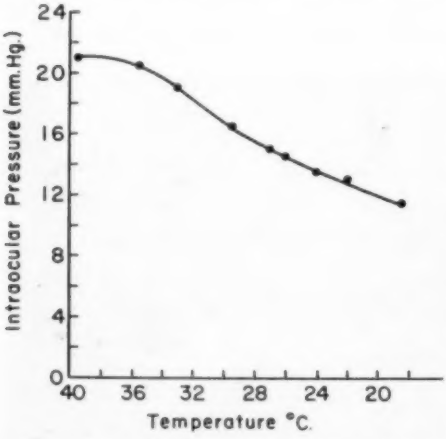

Fig. 2 (Pollack, Becker and Constant). Fall in intraocular pressure with fall in rectal temperature (linear plot).

Tonographic data from 11 rabbit eyes in the normothermic and the hypothermic states are tabulated in Table 2. The facility of outflow decreased from 0.37 µl/min./mm. Hg in the normothermic rabbit (C_N) to 0.24 µl/min./mm. Hg in the hypothermic rabbit (C_H) at 19.1°C. However, this change could be entirely accounted for by the increased viscosity of water at this lower temperature. Thus appropriate adjustments to 39.5°C. for this viscosity change (C_{vis}) are included in Table 2 for comparison. From these data aqueous flow was calculated to be decreased (ΔF) by an average of (mean ± S.D.) 88 ± 6.8 percent following hypothermia. Typical tonograms are shown to illustrate the tonographic tracing obtained from an eye of a rabbit in the normothermic state (40°C.) and from the same eye under hypothermia (20°C.) (fig. 4).

Perfusion experiments confirmed the decrease in outflow facility that was observed during tonographic studies of hypothermic rabbits (table 3). The facility of outflow obtained by perfusion in vivo of 14 hypothermic rabbit eyes was 0.24 ± 0.08 (mean ± S.D.) and agreed well with the facility of outflow obtained by perfusion in vitro (0.23 ± 0.06) and by tonography (0.24 ± 0.08).

The facility of outflow during hypothermia changed by an amount that appeared to be entirely accounted for by variations in the viscosity of water with temperature. One could calculate flow rates from the intra-

TABLE 2

COMPARISON OF INTRAOCULAR PRESSURE AND FACILITY OF OUTFLOW IN NORMOTHERMIC AND HYPOTHERMIC RABBITS AS DETERMINED BY TONOGRAPHY

Rabbit No.		Normothermia			Hypothermia				
		Temperature °C.	P_1	C_N	Temperature °C.	P_2	C_H	C_{vis}	$\Delta F\%$
32	O.D.	39.5	25.5	0.50	16.5	13.0	0.23	0.39	− 89
32	O.S.	39.5	23.5	0.38	16.5	12.0	0.30	0.50	− 84
P16	O.D.	39.0	23.5	0.42	18.0	14.5	0.24	0.38	− 78
P16	O.S.	39.0	21.5	0.31	18.0	12.5	0.19	0.31	− 83
P13	O.D.	39.5	23.0	0.33	19.0	12.0	0.23	0.36	− 85
P13	O.S.	39.5	25.5	0.34	19.0	10.0	0.21	0.33	− 96
P15	O.D.	40.0	17.5	0.34	20.0	8.0	0.31	0.47	−100
P15	O.S.	40.0	18.0	0.37	20.0	11.0	0.23	0.35	− 86
31	O.D.	40.0	17.0	0.40	21.0	10.0	0.25	0.30	− 92
31	O.S.	40.0	23.0	0.45	21.0	11.0	0.26	0.31	− 92
P14	O.S.	39.5	20.5	0.20	21.0	11.0	0.23	0.34	− 80
Mean		39.5	21.9	0.37	19.1	11.4	0.24	0.37	− 88
S.D.			3.4	0.08		1.7	0.04	0.07	± 6.8

P_1 = Intraocular pressure in the normothermic rabbit eye (mm.Hg)
C_N = Facility of outflow in the normothermic rabbit eye (μl./min./mm.Hg)
P_2 = Intraocular pressure in the hypothermic rabbit eye (mm.Hg)
C_H = Facility of outflow in the hypothermic rabbit eye (μl./min./mm.Hg)
C_{vis} = Facility of outflow in the hypothermic rabbit eye adjusted to 39.5°C. for viscosity changes (μl./min./mm.Hg)
$\Delta F\%$ = Percent change in aqueous flow

$$= 100 \frac{(P_2-9)C_H-(P_1-9)C_N}{(P_1-9)C_N}$$

ocular pressure data summarized in Table 1. This rate of flow, expressed as a percent of the control value, was found to fall exponentially with the fall in rectal temperature (fig. 5). For every 7°C. fall in temperature the flow rate was halved.

TABLE 3

FACILITY OF OUTFLOW UNDER HYPOTHERMIA AS ESTIMATED BY PERFUSION OF RABBIT EYE

	In Vivo			In Vitro*	
Temperature °C.	Po	C_H	C_{vis}	C_H	C_{vis}
15.0	13.5	0.13	0.23	0.17	0.26
16.5	11.0	0.22	0.36	0.15	0.23
19.5	8.0	0.19	0.29	0.25	0.38
21.0	11.5	0.24	0.36	0.30	0.46
21.0	8.0	0.42	0.61	0.29	0.44
21.0	8.5	0.29	0.43		
22.0	10.0	0.19	0.28	0.22	0.34
22.0	8.0	0.25	0.36		
22.0	9.5	0.32	0.46		
23.0	9.5	0.33	0.50		
23.0	11.0	0.15	0.21		
23.0	8.5	0.23	0.32		
24.0	12.0	0.13	0.19		
24.0	11.0	0.24	0.33		
Mean 21.2	10.0	0.24	0.35	0.23	0.35
S.D.		0.08	0.12	0.06	0.09

Po = Intraocular pressure in the cannulated eye.
C_{vis} = Facility of outflow adjusted to 39.5°C. for viscosity.
C_H = Facility of outflow in the hypothermic rabbit eye.
* At temperature 20°C.

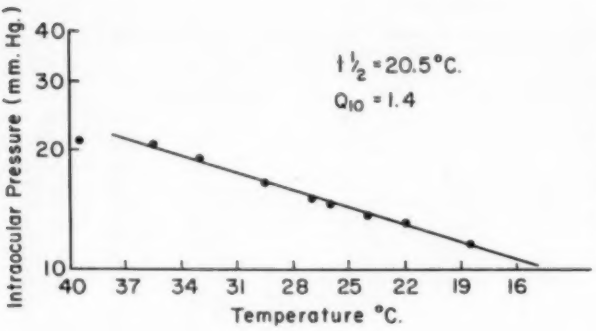

Fig. 3 (Pollack, Becker and Constant). Fall in intraocular pressure with fall in rectal temperature (semi-log plot). For every 20.5°C. fall in temperature the pressure decreases 50 percent. The temperature coefficient, Q_{10}, is 1.4.

Discussion

A progressive decrease in intraocular pressure is found to occur with a fall in the rectal temperature of rabbits (table 1). The exponential plot for this process reveals a straight line whose slope suggests a 3.4% fall in pressure per degree centigrade decrease in temperature (fig. 3). It is interesting to note that a similar, though faster (5.6 percent/°C.), fall in cerebrospinal fluid pressure has also been observed.[14] The first significant decline in intraocular pressure is observed at 33°C. ($p = .05$). Other investigators studying the effect of hypothermia on physiological functions have noted similarly that the initial fall below the control value occurs between 32° and 35°C.[2,12-14] It has been suggested that this delay is due to shivering occurring during the induction period.[2,13]

Tonographic data (table 2) reveal a fall in intraocular pressure from 21.9 mm. Hg in the normothermic state to 11.4 mm. Hg under hypothermia (average temperature of 19.1°C.). The facility of outflow falls from a mean value of 0.37 µl/min./mm. Hg in the normothermic animal to 0.24 µl/min./mm. Hg in the hypothermic animal. Perfusion erperiments further confirm the decrease in outflow facility during hypothermia. When the values for the facility of outflow in the hypothermic animal are appropriately adjusted for viscosity changes, the adjusted facility has a mean value of

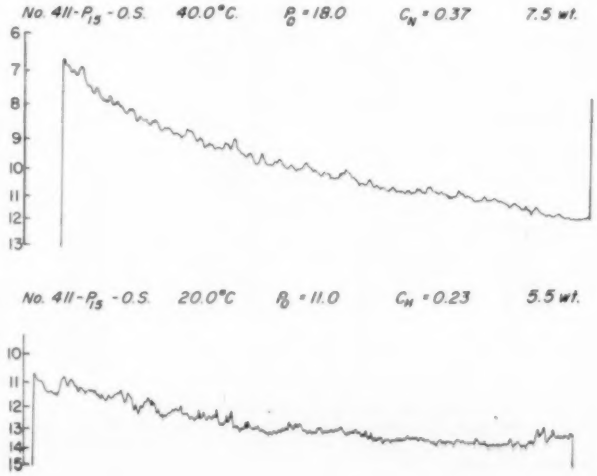

Fig. 4 (Pollack, Becker and Constant). Tonographic tracings of rabbit eyes before (upper) and after (lower) hypothermia. Intraocular pressure is reduced from 18 mm. Hg to 11 mm. Hg and facility of outflow falls from 0.37 µl/min./mm. Hg (C_N) to 0.23 µl/min./mm. Hg (C_H). Facility of outflow under hypothermia adjusted for viscosity change (C_{T11}) would be 0.35 µl/min./mm. Hg.

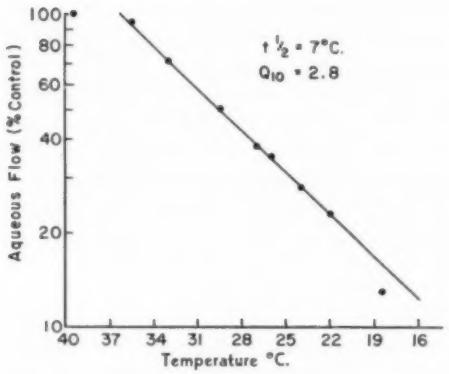

Fig. 5 (Pollack, Becker and Constant). Fall in rate of aqueous flow (expressed as a percentage of the control value) with decrease in rectal temperature (semilog plot). Temperature is halved every 7°C. fall in temperature. The temperature coefficient (Q_{10}) is 2.8.

0.37 µl/min./mm. Hg and is not statistically different from the mean value for the normothermic rabbit (tables 1 and 2).

From tonometric measurements of rabbit eyes during hypothermia aqueous flow is calculated to be approximately 50 percent of the control value when the rectal temperature is 29.5°C. (fig. 5). At 19°C. there is an 83% decrease in flow which further confirms the decrease in flow that is found by tonography (88 percent at 19.1°C., table 2). The temperature coefficient, Q_{10}, of this process is 2.8. An Arrhenius temperature plot reveals an exponential relationship between the fall in flow rate and the reciprocal of the absolute temperatures; the activation energy, E, being about + 18,000 cal./mol. This figure is similar to the activation energy described by Blatteis[15] for glomerular filtration rate (below 25°C., E = +16,958 cal./mol.), renal plasma flow (E = +19,708 cal./mol.), and tubular excretion of para-aminohippurate (PAH) (E = +18,250 cal./mol.); and by Page[13] for tubular excretion of PAH (Q_{10} = 3.62, E = +23,540 cal./mol.).

The flow data for 18.5°C. (fig. 5) does not fall on the line. This may be due to many complicating factors that may occur in the deeply hypothermic animal including poor respirations, hypoxia, and circulatory changes. Other sources of error include the possibly of less accurate interpretation of tonometer readings as well as alterations in scleral rigidity and corneal indentation with tonometry under hypothermia.

It would appear that cold exerts a depressant action upon the ciliary body resulting in a fall in aqueous secretion. The mechanism for this, however, can only by speculated upon at the present time. It is conceivable that a reduction in ciliary body blood flow contributes to a depression in aqueous secretion. Such a reduction might follow in the wake of the fall in arterial blood pressure, the decrease in cardiac output, and the increase in blood viscosity which occur during hypothermia.[2] A possible rise in vascular resistance in the ciliary body would further decrease blood flow and complete a picture that is quite similar to that which has been suggested to explain the reduction in renal blood flow during hypothermia.[15, 16] Direct inhibition by cold of enzymatic processes responsible for aqueous secretion may be an important factor. Paralysis of certain renal tubular transport mechanisms (for example, glucose reabsoption) during hypothermia have already been demonstrated.[17] The relationship of a depressed central nervous system[18] to ciliary body secretion must also be considered and needs to be investigated.

Turnover studies of various substances in the hypothermic rabbit are in progress and may shed new light on the transport mechanism of the ciliary body. Studies of the ciliary body architecture during hypothermia are completed and offer additional data for reconstructing the process of aqueous secretion. It is hoped that immersion hypothermia may prove a valuable adjunct for the study of aqueous humor dynamics.

Summary

Intraocular pressure fell logarithmically

with decline in rectal temperature during immersion hypothermia in rabbits. The first significant fall appeared at 33°C. and the pressure was halved for every 20.5°C. fall in body temperature thereafter. The temperature coefficient (Q_{10}) of this process was found to be 1.4.

A decrease in the facility of outflow occurred during hypothermia as demonstrated by tonography and perfusion in vivo and in vitro. However, this fall could be entirely accounted for by the changes in viscosity of water with temperature.

Aqueous flow decreased 80 to 90 percent at 19°C. as estimated by comparative tonometric and tonographic studies of normothermic and hypothermic rabbits. For every 7°C. fall in body temperature, the flow rate was halved.

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Discussion

DR. E. J. BALLINTINE (Cleveland): How do you correct the coefficient of outflow for change in viscosity in the intraocular fluid?

DR. POLLACK: One can determine, from tables that have already been calculated, the changes in viscosity that can be expected of the fluids at various temperatures.

DR. BALLINTINE: I know that, but how do you apply this to the coefficient of outflow?

DR. POLLACK: By multiplying with the coefficient that you use.

DR. BALLINTINE: In other words, you assume that the coefficient of outflow is proportional to the viscosity?

DR. POLLACK: No. If one takes the facility of outflow at this lower temperature and uses this fac-

tor, one finds that the change in facility of outflow can be entirely accounted for by the change in viscosity of the fluids.

DR. BALLINTINE: I want to know how you apply Poiseuille's law to this situation. I presume that is the way you do it, but I would like to know the details if they are available. It is not apparent to me just how you do it.

DR. BECKER: If the difference between viscosity of water at 25°C. and 39.5°C is a difference of 30 percent, then one can take the outflow facility at 25°C. and multiply it by 1.3 and compare this with the 39.5°C. reading.

DR. BALLINTINE: In other words, the amount of fluid transmitted is inversely proportional to the viscosity?

DR. BECKER: This is the assumption Dr. Grant used in correcting the room temperature perfusions back to body temperature for comparison.

DR. BALLINTINE: And you assume the transmission is inversely proportional to viscosity?

DR. BECKER: Facility is inversely proportional to viscosity.

DR. BALLINTINE: How do you know that the viscosity coefficient of aqueous humor with temperature is the same as it is for water?

DR. BECKER: It is the viscosity of water that is used, You don't know it, but for the purposes of this sort of study the errors by making this assumption are likely to be very small.

DR. BALLINTINE: The second question: From the good correlation that you presented, I presume that the scleral rigidity is not changed by temperature. That is the assumption here, and yet when the viscosity of water changes I would think the elastic properties in the sclera would change by a similar amount.

DR. BECKER: If these changes occur, they are apparently compensated or are not of significant magnitude to effect the measurement.

DR. BALLINTINE: That is what I would like to know. Do they change? It seems incredible that the tissue would maintain the same elasticity at this temperature. In other words, the rabbit becomes stiff, and I see no reason why the sclera would not get stiff, too. Apparently it does not.

DR. BECKER: There are several possibilities. One is that changes may occur and be compensated. A second is that they may occur but be of insufficient magnitude to be measured. Third, they might occur in some exponentials. I don't know how to distinguish among these at the present time.

DR. BALLINTINE: You could measure the coefficient of scleral rigidity simply by taking the measurement of the eye—

DR. BECKER: Dr. Grant may have some data on this. Morton, does it make any difference whether you measure scleral rigidity at 20°C. or at 37°C.?

DR. W. MORTON GRANT (Boston): Unfortunately I haven't determined that yet. I have had it in mind to do.

The question about the variation of facility of outflow with temperature in perfused enucleated eyes I have investigated experimentally, and I find that the facility of outflow varies inversely with the viscosity of saline. I wonder whether it has been determined that the viscosity of blood varies in the same manner as the viscosity of water or saline with temperature.

DR. BECKER: That is well known. Viscosity of blood varies very much more with temperature than does that of saline, particularly in vivo, because in vivo one has multiple factors that determine viscosity.

In the first place, there is hemoconcentration in vivo. Besides that, even in vitro blood viscosity changes very much more than water does. This may be a mechanism by which blood supply is reduced to the ciliary body.

DR. GRANT: Your nice results rather suggest that the blood in the outflow channels can't occupy a very large proportion of the channels or else facility of outflow would become less.

DR. BECKER: Yes, unless again we are dealing with compensating errors, as Dr. Ballintine points out. The facility of outflow as measured is less, and we can explain this on the basis of viscosity changes of water; but there are other possible explanations, too.

DR. MAURICE E. LANGHAM (Baltimore): I would like to ask Dr. Pollack three questions.

First, was the blood pressure of these experimental animals measured and if so what was the effect of falling temperature on the blood pressure.

Secondly, have you investigated the effect of hypothermia on the ascorbic acid transfer into the aqueous humour as this could give one some idea of the changes of blood flow through the eye.

Thirdly, have you measured the changes of intraocular pressure when cold fluid is applied directly to the surface of the eye? In this connection, I have recently observed that if ice cold saline is dripped on the cornea, the temperature of the aqueous can be brought down to below 10°C. within a minute or two and that under these conditions the intraocular pressure increases by 3.0 to 4.0 mm. Hg.

DR. POLLACK: In answer to your first question, there is not entirely good agreement that the blood pressure in dogs does fall with fall in body temperature.

Several investigators have stated that blood pressure does not change significantly, especially in the early period of lowering body temperature. One of the reasons postulated for this is that although cardiac output decreases during hypothermia, the vascular resistance increases. However, at some point vascular resistance in the body does decrease and with it there is a concomitant fall in blood pressure.

Studies in the dog that we have done show that the systemic blood pressure is maintained even after intraocular pressure has begun to fall. It is true, however, that soon the blood pressure does fall and the intraocular pressure continues to decrease.

In answer to the last question, yes, we have done a few preliminary studies of dropping ice water on corneas in a few patients and rabbits. The patients on whom we have done this had uncontrollable glaucoma and Schiøtz pressures were taken in effort to

determine any possible drop in intraocular pressure.

Our results, however, were of limited success. This may have been due to the fact that we were not efficiently cooling the site—or the blood to the site—of secretion in the eye.

DR. BECKER: I would like to answer the other question and would like to comment on the blood pressure question, too.

In the first place, if blood pressure fell (and it does fall), this would produce a sudden effect on intraocular pressure. Then one would develop a new steady state, and pressure should not be altered.

These animals were maintained hypothermic for six or eight hours, and maintained a steady state. If there are blood pressure effects this is not what we are measuring at this late time. When you press the carotid you get a fall in intraocular pressure, but the pressure comes back up even if the carotid is occluded.

On the other hand, the effect may be dependent on blood flow, as has been postulated in the kidney. Much of the impaired kidney function may be due to reduction in blood flow to the kidney. For the eye, we would like very much to use the Linnér method for measuring blood flow. Unfortunately we run into the same problems as in trying to use the para-aminohippurate method for measuring renal blood flow in the hypothermic animal. The transport of both ascorbate and para-aminohippurate are impaired by hypothermia so the methods are not useable.

The third point, about cold water on the eye, is reminiscent of why Diamox does not act when you drop it on the eye. The ciliary body has a tremendous blood supply, and it is coming in at 39°C. and flowing through reasonably rapidly.

DR. WOLTER: I remember giving a white rabbit to my children last summer to play with—which they exposed to cold water. The rabbit died shortly after just from being all wet and cold.

I wonder whether the reaction of your rabbits to the cold water can be understood as something like a collapse or an early phase of death. Did the rabbits survive?

DR. POLLACK: Yes. In our experiments rabbits are used throughout the procedure. Many of these rabbits will live. In some of the experiments after working with rabbits under hypothermia, they were placed back in their cages where they survived several days.

Also, these rabbits aren't just dipped in water, as your rabbit might have been. Ours are given a general anesthetic and are asleep. It is true that sometimes anesthesia is necessary until cold narcosis takes over. Cold narcosis usually takes over at about 30°C., after which time you don't need any more anesthesia.

So, the rabbit isn't really awake much of the time, and sometimes not at all. On occasion we don't have to give the rabbit a booster dose.

DR. WOLTER: I thought they might have actually been in the early stage of dying.

DR. BECKER: There is a close relationship between hypothermia and death.

THE EFFECT OF HYPOTHERMIA ON AQUEOUS HUMOR DYNAMICS*

II. ULTRASTRUCTURAL CHANGES IN THE RABBIT CILIARY EPITHELIUM

ÅKE HOLMBERG,† M.D., AND BERNARD BECKER, M.D.
Saint Louis, Missouri

INTRODUCTION

The ultrastructure of the ciliary epithelium of normal and acetazolamide treated rabbit, monkey and human eyes has been described.[2-4] Remarkable changes in the epithelium were observed to accompany the alterations in rate of secretion of aqueous humor.

Recently systemic hypothermia in rabbits has been demonstrated to reduce the rate of formation of aqueous humor.[1] The secretory rate was found to decline exponentially with fall in rectal temperature, so that at 27°C. it was approximately 50 percent of normal, and at 20°C. it was reduced to some 10 to 20 percent of normothermic levels. Similar degrees of suppression were measured by both tonographic and turnover studies. The present study was undertaken to evaluate the fine structure of the ciliary epithelium when secretion of aqueous humor was decreased by systemic hypothermia, and to compare the changes with those observed following acetazolamide administration.

* From the Departments of Ophthalmology and Anatomy and the Oscar Johnson Institute, Washington University School of Medicine. This investigation was supported in part by a research grant, B-621, from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

† Fight for Sight Fellow of the National Council to Combat Blindness.

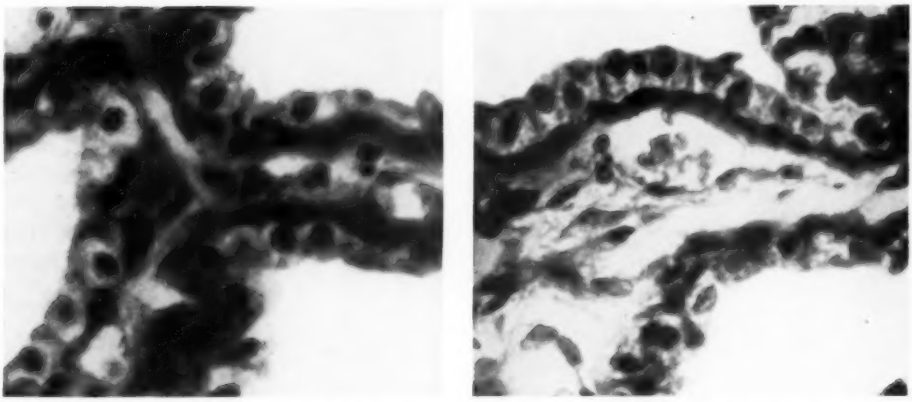

Fig. 1 (Holmberg and Becker). Light micrographs of the ciliary epithelium in normal (left) and hypothermic rabbit (right). Note marked reduction in size of pigmented layer during hypothermia. (×540.)

Material and Methods

Immersion techniques were used to cool the animals, as described previously.[1] Ten eyes from six albino rabbits were examined, including two control eyes, two eyes at 27°C. and six eyes at 20°C. For light microscopy parts of the ciliary body were fixed in formalin, embedded in paraffin, sectioned at 5.0 μ, and stained with various techniques. For electron microscopy parts of the ciliary body from the same eyes were fixed in osmium solution for two hours, dehydrated and embedded in methacrylate, according to techniques routinely used in electron microscopy. Sections were cut on a Porter-Blum microtome and examined in RCA EMU 2e microscope.

Results

A. Light microscopic appearance of the ciliary epithelium during hypothermia

During hypothermia at 20°C. a considerable reduction in the size of the cells in the pigment layer was observed (fig. 1). In some areas of the ciliary epithelium this layer measured only 1.0 μ in thickness, while in the normal animals it measured 4.0 to 6.0 μ. No other specific differences between normothermic and hypothermic ciliary bodies were observed with the light microscope.

B. Electron microscopic appearance of the ciliary epithelium during hypothermia

The decrease in size of the pigment epitheluim was also recognized in the electron microscope. In addition, interesting changes in the fine structure of the epithelium were observed during hypothermia. These consisted of a thickening of the mitochondria and a definite increase in the number of small vesicles in the cytoplasm.

1. *Mitochondria.* Table 1 sumarizes the estimated width of the mitochondria in the ciliary epithelium at 27°C. and 20°C. compared with the normothermic and acetazolamide-treated rabbit. During hypothermia a remarkable and statistically significant increase in the size of the mitochondria of both epithelial layers was noted. The mitochrondria of the nonpigmented layer were increased to a greater extent than that of the pigmented layer. As can be seen in Figures 2 and 3 the alterations in mitochondria took place without change in the normal density of the mitochondrial matrix. The fine structure of the mitochondria demonstrated no changes whatsoever as to appearance, size

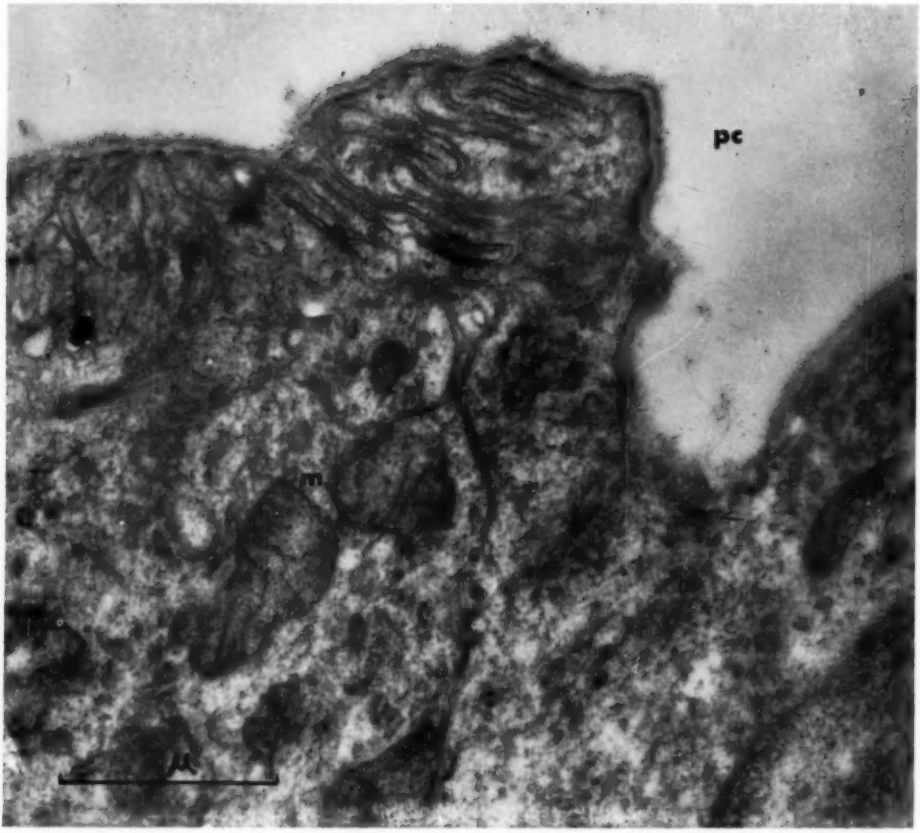

Fig. 2 (Holmberg and Becker). Part of a nonpigmented cell of ciliary epithelium from a normal rabbit. pc = posterior chamber. m = mitochondria (×33,000.)

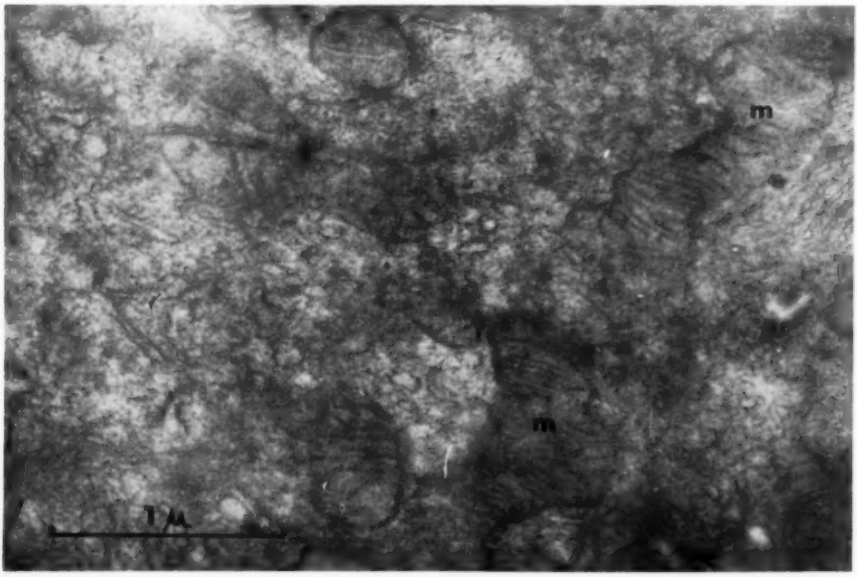

Fig. 3 (Holmberg and Becker). Mitochondria (m) in a nonpigmented cell of ciliary epithelium from a rabbit during hypothermia at 20°C. Although the mitochondria has increased in size, the staining density of the mitochondrial matrix is the same as in normal material. Compare with Figure 2. (×35,000.)

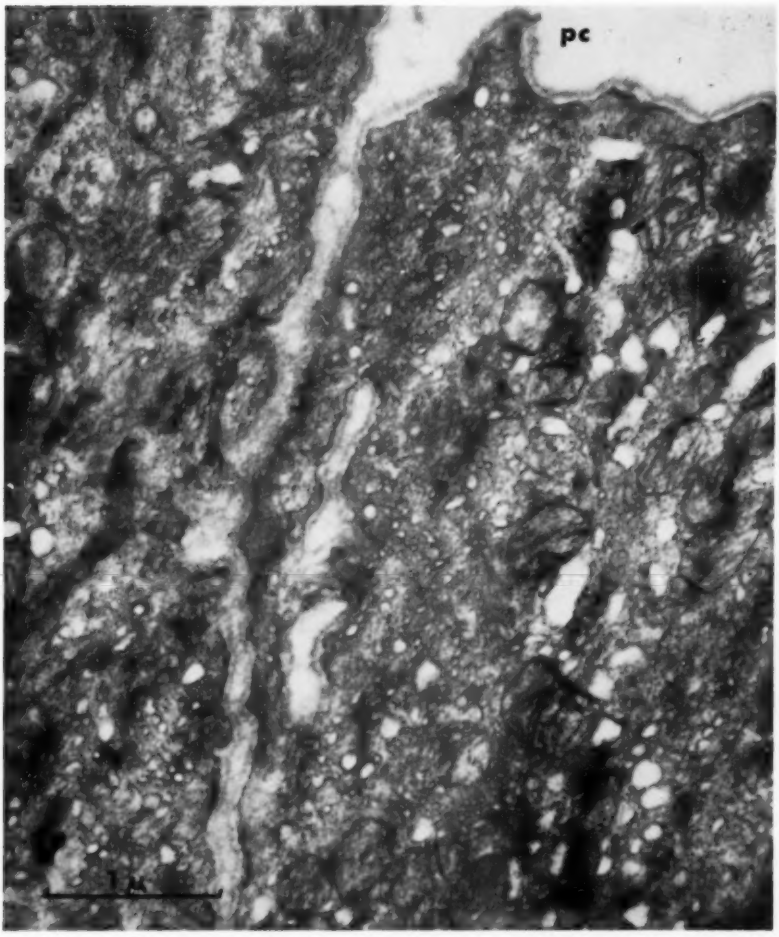

Fig. 4 (Holmberg and Becker). Part of a nonpigmented cell of ciliary epithelium from a rabbit during hypothermia at 20°C. Note the large number of vesicles in the cytoplasm. pc = posterior chamber. Compare with Figure 2. (×26,500.)

and composition of the outer and inner membranes.

2. *Vesicles.* Small vesicles have been described in the ground substance of the cytoplasm of both layers of the normal ciliary epithelium.[3] During hypothermia at 27°C. and 20°C. the number of these vesicles was increased considerably (figs. 4 and 5). Although the increase occurred in both layers, the accumulation of vesicles was more pronounced in the nonpigmented epithelium (table 2). Close to the posterior chamber surface of the nonpigmented cells during hypothermia, the vesicles tended to become arranged in rows in a regular fashion (fig. 5). This occurred more frequently at 20°C. and especially after prolonged hypothermia.

Besides the accumulation of vesicles observed in both layers, one occasionally encountered large vacuoles in the basal part of the pigment epithelium (fig. 6). They occupied comparatively large areas and in

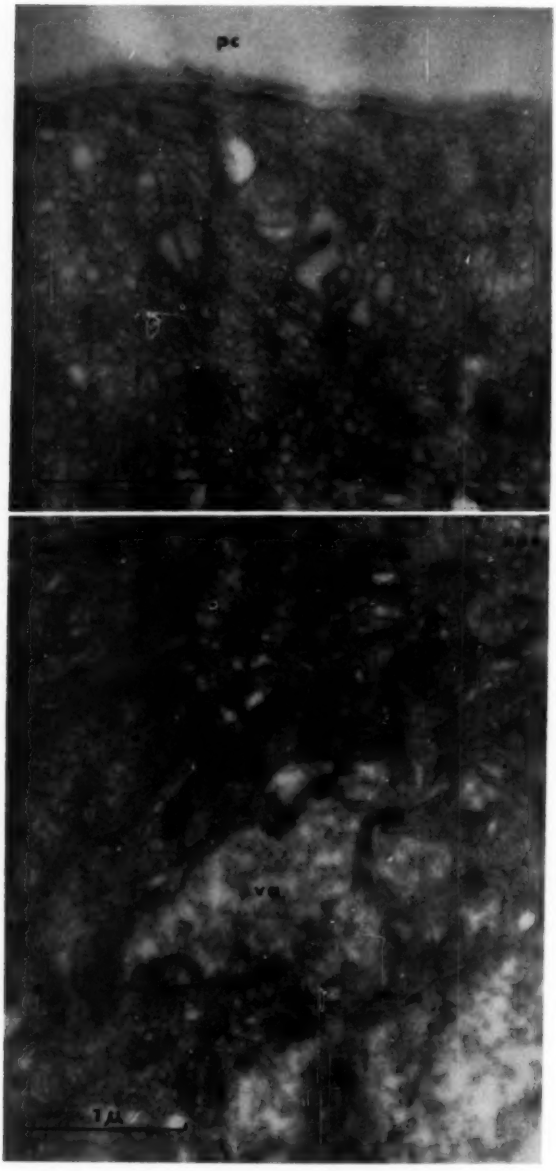

Fig. 5 (Holmberg and Becker). Part of a nonpigmented cell of ciliary epithelium from a rabbit under hypothermia at 20°C. Next to the surface of the cell (pc = posterior chamber) the vesicles are arranged in rows. (×42,000.)

Fig. 6 (Holmberg and Becker). Part of a pigmented cell (pe) of ciliary epithelium from a rabbit under hypothermia at 20°C. A large vacuole (va) containing granular material is visible. npe = nonpigmented epithelium. (×36,000.)

TABLE 1

ALTERATIONS IN THICKNESS OF THE MITOCHONDRIA IN RABBIT CILIARY EPITHELIUM

Treatment	Thickness* (μ)	
	Nonpigmented Epithelium	Pigment Epithelium
Normal	0.18 ± 0.005	0.17 ± 0.006
Acetazolamide[3]	0.26 ± 0.008	0.16 ± 0.006
Hypothermia 27°C.	0.30 ± 0.029	0.22 ± 0.007
Hypothermia 20°C.	0.29 ± 0.016	0.22 ± 0.014

* Mean ± SEM.

TABLE 2

THE FREQUENCY OF VESICLES IN THE RABBIT NONPIGMENTED CILIARY EPITHELIUM

Treatment	Number* of Vesicles per 0.05μ^2
Normal	0.79 ± 0.102
Acetazolamide 15 min.[3]	2.85 ± 0.273
Hypothermia 27°C.	1.51 ± 0.205
Hypothermia 20°C.	1.74 ± 0.385

* Mean ± SEM.

some instances they seemed to be formed by enlargement of the light central space of the β-cytomembranes.[3] In other instances they were located between two adjacent pigmented cells. The large vacuoles contained granular material.

DISCUSSION

Hypothermia and carbonic anhydrase inhibitors offer two different methods by which the secretion of aqueous humor can be partially inhibited. The effects of acetazolamide on the ciliary epithelium have been analyzed previously.[2-5] It was found that acetazolamide produced an increase in the thickness of the mitochondria and an accumulation of small vesicles in the rabbit nonpigmented epithelium. It is most interesting to note that hypothermia produced much the same changes in the nonpigmented layer. There are small differences however. Hypothermia has a more marked effect on the size of the mitochondria (table 1), but produces less dramatic accumulation of vesicles than follows acetazolamide (table 2). Furthermore hypothermia affects the pigmented as well as the nonpigmented layer, whereas the acetazolamide effects are confined entirely to the nonpigmented epithelium. These findings are in accord with the more specific effects of carbonic anhydrase inhibitors on the ciliary epithelium and the more generalized metabolic effects of temperature depression.

It should be emphasized that the alterations observed in the mitochondria do not resemble the clearing of the ground substance as seen in simple swelling or delayed fixation. In the present as well as in the acetazolamide-treated material, all mitochondria show a ground substance with an osmiophilic staining density similar to that of normal mitochondria.

The physiologic interpretation of the morphologic changes observed in the ciliary epithelium remains speculative at present. Alterations in size of mitochondria suggest metabolic changes in the secretory cells and appear to correlate with functional status. Cytoplasmic vesicles of the rabbit nonpigmented epithelium appear to increase during hyposecretion induced by a variety of methods. These changes may relate to a possible role of pinocytosis in aqueous secretion. The functional significance of the changes in the rabbit pigmented epithelium during hypothermia remains obscure and is the subject of current investigation.

SUMMARY

The decrease in the rate of aqueous humor secretion induced by systemic hypothermia in rabbits was found to be associated with changes in the fine structure of the ciliary epithelium. The alterations in the nonpigmented epithelium resembled those following acetazolamide administration, consisting of increased size of the mitochondria and accumulation of cytoplasmic vesicles. In contrast to the absence of alterations in the pigmented epithelium of the rabbit eye following carbonic anhydrase inhibition, hypothermia resulted in a reduction in the size of the cells, thickening of the mitochondria,

and an increased vesiculation of the cytoplasm of this layer.

610 South Kingshighway (10).

ACKNOWLEDGMENT

The sections for light microscopy were prepared by Dr. Johannes Rohen.

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DISCUSSION

DR. WOLTER (Ann Arbor): One of the classic changes seen in prolonged hypotonia—for example following a fistula of the cornea—is the appearance of clear vacuoles in the nonpigmented layer of the ciliary body epithelium. This has been produced in animal experiments, I believe, by Dr. Rohen who now works with you in Saint Louis. I wonder whether the vacuoles which you found after hypothermia are anything like those in hypotonia.

DR. WERNER NOELL (Buffalo): Dr. Holmberg, I was puzzled by your differentiation between growth and swelling of the mitochondria. I wonder whether you could give me a justification for your use of the word "growth."

My second question is related to this. I wonder whether you tested isolated mitochondria. I ask this with regard to the studies by Hunter, et al. (J. Biol, Chem., **234**:2176, 1959) on the swelling of isolated mitochondria relative to the activities of the electron transport chain.

DR. HOLMBERG: First I will comment on Dr. Wolter's remarks. I think we are dealing with two different conditions. The changes you are talking about occur in hypotony after paracentesis of the eye.

The condition I am talking about is hyposecretion, and I think it is something entirely different. We certainly don't see any large vesicles after hypothermia.

What we can say about the electron microscopic appearance of the mitochondria is that there is an increase in size but no change in the density of the ground substance. This is what we see.

I know nothing about the effect of hypothermia on isolated mitochondria. Nothing has been done on it.

The mitochondria swell postmortem but this swelling is accompanied by a loss or clearing of the ground substance. Under hypothermia the mitochondria also swell but the density of the ground substance remains normal. The difference is very obvious.

DR. NOELL: Do you imply that more ground substance was formed?

DR. HOLMBERG: If the swelling were due to an uptake of water only I would expect to get a decrease or clearing of the ground substance.

DR. NOELL: I am in no position to know but does not the increase in size and electron density mean that somehow there is more osmium bound per mitochondrion?

DR. HOLMBERG: Yes that is what we see.

DR. NOELL: I would be skeptical that that is growth.

DR. HOLMBERG: I used the word "growth" in opposition to the simple swelling we see, for instance in postmortem changes of the mitochondria.

VERGENCE AND ACCOMMODATION*

IV. EFFECT OF LUMINANCE QUANTITY ON THE AC/A

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INTRODUCTION

The human eye has an extremely facile focusing adjustment which allows for clear vision of objects at various distances. In previous studies it has been shown that the extent the eye is capable of varying its

* From the Department of Ophthalmology, The University of Michigan Medical School. Assisted by a grant from the Institute of Industrial Health, The University of Michigan.

focus in order to see objects at close distances, that is, its amplitude of accommodation, is dependent upon the background luminance of the object of regard.[1,2] As the background luminance level is gradually reduced the amplitude of accommodation becomes smaller. The phenomenon, so-called "night presbyopia," has been known for some time[3,4] but only a comparatively few precise studies have been made of it. Figure 1 illustrates the mean of the measurements made on four young adult male observers. These data were obtained by measuring the accommodation response to the entire gamut of accommodation stimuli at a number of different luminance levels. All of these measurements were made through a two-mm. artificial pupil centered before the observer's eye. This represents a lower limit of natural pupil size and thus results in the figure cannot be attributed to such factors as variation in spherical aberration and optical or perceptual variation in depth of field. The data can only be explained as a real decrement in the ability of the eye to vary its dioptric power as the visibility of the target against its background is reduced.[1]

In order to learn as much as possible about this effect it seemed desirable to compare it to two other situations in which the amplitude of accommodation is reduced: (a) cycloplegia and (b) the normal process of aging.

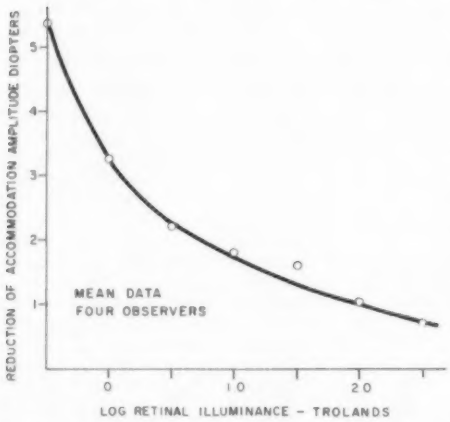

Fig. 1 (Alpern and Larson). The reduction of the amplitude of accommodation in four subjects as a function of the retinal illuminance. The accommodation response was determined over the entire gamut of accommodation stimuli at a variety of different luminance levels, with a subjective optometer.[1]

While these latter two situations have many characteristics in common they differ in the way two concomitant variables (that is, the size of the pupil and the AC/A ratio) change as the amplitude of accommodation is reduced.

In the normal process of aging the reduction of the amplitude of accommodation is related to a progressive decrease in the diameter of the pupil which enhances the depth of field.[5] On the other hand, atropine-like substances which produce temporary cycloplegia usually also produce a concomitant mydriasis. In this respect reduction of the amplitude with the reduction of background luminance is much more like a "night cycloplegia" than a "night presbyopia" since here again the reduced amplitude is associated with a gradually increasing pupil size.

In order to pursue this matter further the present study was devoted to a consideration of the way in which the AC/A changes with the level of background luminance. The AC/A has been defined in a previous paper in this series.[6] It is, theoretically, the amount of innervation to accommodation vergence associated with a unit change in innervation to accommodation. Operationally, it is the amount of change in horizontal heterophoria associated with a unit change in accommodation (provided the measurements are made within the range of stimulus values within which the relation between the accommodation stimulus and its response is linear).

Procedure

Measurements were made on six normal prepresbyopic adult males. The AC/A was obtained by measuring the accommodation in play and the associated phoria at a number of different stimulus levels of accommodation using the haploscope and a procedure which has been described in detail in

a previous paper.[7] Three measurements of accommodation response and phoria were obtained at each of five different (1-5D) stimulus levels of accommodation. In this way the relative positions of the lines of sight of the two eyes was determined when the eye accommodated different amounts. These measurements were then repeated, in separate experimental sessions, at different light levels ranging in one-half log steps from 3.8×10^2 to 0.038 trolands of retinal illuminance. All data were obtained while the observer viewed the chart with the right eye through a two mm. in diameter artificial pupil. The statistical procedures already described[6] for the determination of the best fitting straight line for the data showing the phoria values at each accommodation response were employed.

The test object was a Snellen acuity chart, 340 cm. from the eye, illuminated by a 300-watt tungsten filament lamp mounted in a projector. Wratten No. 96 (neutral) filters in front of the projector and/or the eye were used to vary the light level. The sizes of the test letters were varied so that, as the luminance of the background decreased, letters at the threshold of visibility were always in view. The room was carefully screened so that stray light from the source did not enter the observer's eye.

Results

The relationship between the measured horizontal heterophoria and the amount of accommodation in play (over the range of accommodation stimuli used for the present observers) can for each observer and each experimental session be plotted as a sloping straight line showing increasing phoria as accommodation is increased. If the phoria (vergence) is plotted on the abscissa then the reciprocal of the slope of this line represents the AC/A, while the intercept of the line with the abscissa axis represents the heterophoria value when the accommodation is extrapolated to zero. These two quantities (and particularly the AC/A) were the subject of the present investigation. However, in the process of computing these, two other statistics were obtained from each experimental session: (a) the rate of change of accommodation as the stimulus to accommodation is changed one diopter, and (b) the rate of change of horizontal phoria as the stimulus to accommodation is changed by one diopter (that is, the stimulus AC/A). The latter two quantities as measured for each observer and luminance level are summarized in Table 1 and Table 2 respectively. The change in accommodation with light level (table 1) has already been the subject of a recent analysis from this laboratory[1] and while the results of the present study differ in some specific details from the previous work, the general features of the two sets of data are remarkably similar and the conclusions drawn from the previous study are substantiated by the present results. The change in stimulus AC/A (Table 2) with

TABLE 1

THE EFFECT OF TARGET LUMINANCE ON THE EFFECTIVITY OF AN ACCOMMODATION STIMULUS TO EVOKE AN ACCOMMODATION RESPONSE

Log I	S. K. N=5	F. Z. N=2	B. O. N=1	B. L. N=3	M. A. N=2	H. D. N=3	M. N.
2.68	0.93	1.00	0.79	1.01	0.83	0.79	0.89
2.19	0.96	0.98	0.94	1.01	0.80	0.82	0.92
1.68	0.84	1.00	0.85	0.92	0.84	0.87	0.89
1.19	0.76	0.91	0.88	0.99	0.91	0.74	0.71
0.68	0.94	0.93	1.12	0.94	0.82	0.74	0.91
0.19	0.82	0.95	0.88	0.99	0.76	0.77	0.86
1.68	0.81		0.03	0.86	0.54	0.66	0.57
1.19	0.31	0.99	0.06	1.08	0.89	0.40	0.60
2.68	0.33		0.04	1.22	0.50	0.74	0.55

TABLE 2

EFFECT OF LUMINANCE ON THE STIMULUS AC/A (DEGREES/DIOPTER)

Log I	S. K. N=5	B. O. N=1	F. Z. N=2	M. A. N=2	H. D. N=3	B. L. N=3	M. N.
2.68	1.56	1.92	1.20	2.72	2.53	2.76	2.11
2.19	1.44	1.91	1.43	2.53	2.53	2.43	2.04
1.68	1.45	2.09	1.28	2.49	2.61	2.29	2.03
1.19	1.48	1.68	1.02	2.92	2.54	2.44	2.01
0.68	1.13	2.84	1.16	2.60	2.10	2.22	2.00
0.19	1.31	1.83	1.24	2.39	2.16	2.06	1.83
1.68	0.81	0.15		1.98	2.04	2.35	1.47
1.19	0.64	0.02	1.14	1.99	0.67	4.14	1.43
2.68	0.44	0.01		1.60	2.63	5.08	1.95

light level in general follows the same trends as the change in the theoretically more important (response) AC/A. For these reasons the discussion which follows will be devoted entirely to the characteristics of the sloping straight line which shows the relation between phoria and the accommodation in play.

The characteristics of this line as measured for each observer at each light level are summarized in Table 3 (AC/A) and Table 4 (phoria).

Figure 2 illustrates typical results from a single session at each light level for one of the observers. In this figure the phoria is plotted along the abscissa, the accommodation response on the ordinate. The data obtained at the highest luminance level (480 trolands) occupies its correct position on the graph. The data obtained at each successively lower light level are shifted five degrees farther to the right on the abscissa than the luminance level immediately higher. Since the reciprocal of the slope of each line represents the AC/A at a different light level, this figure illustrates the fact that for this observer, at least, no very marked change in AC/A occurred as the luminance was gradually lowered.

Figure 3 illustrates the extent to which this is true for each of the observers. Each of the graphs in this figure represents a plot of the AC/A as a function of the logarithm of the retinal illuminance. Recalling

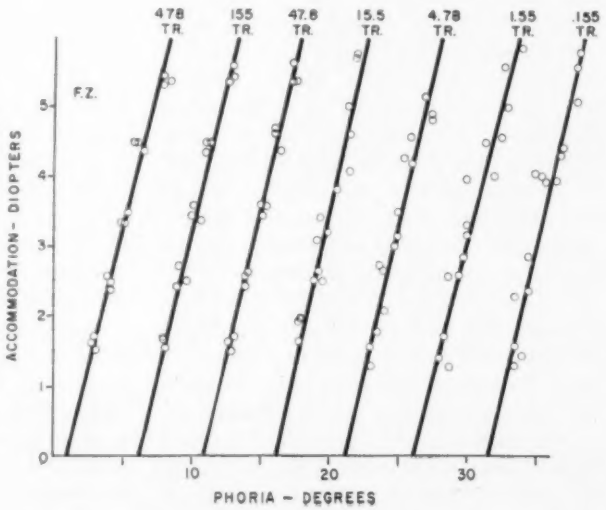

Fig. 2 (Alpern and Larson). The relation between the accommodation and phoria obtained from observer F. Z. at a variety of different light levels. Each point is a single determination. The level of retinal illuminance (in trolands) at which the measurements were made is given at the top of each graph. The data at the highest level are properly positioned on the graph. Those at lower levels are shifted five degrees farther to the right on the abscissa than the measurements made at the light level immediately higher than the level at which the measurements were made.

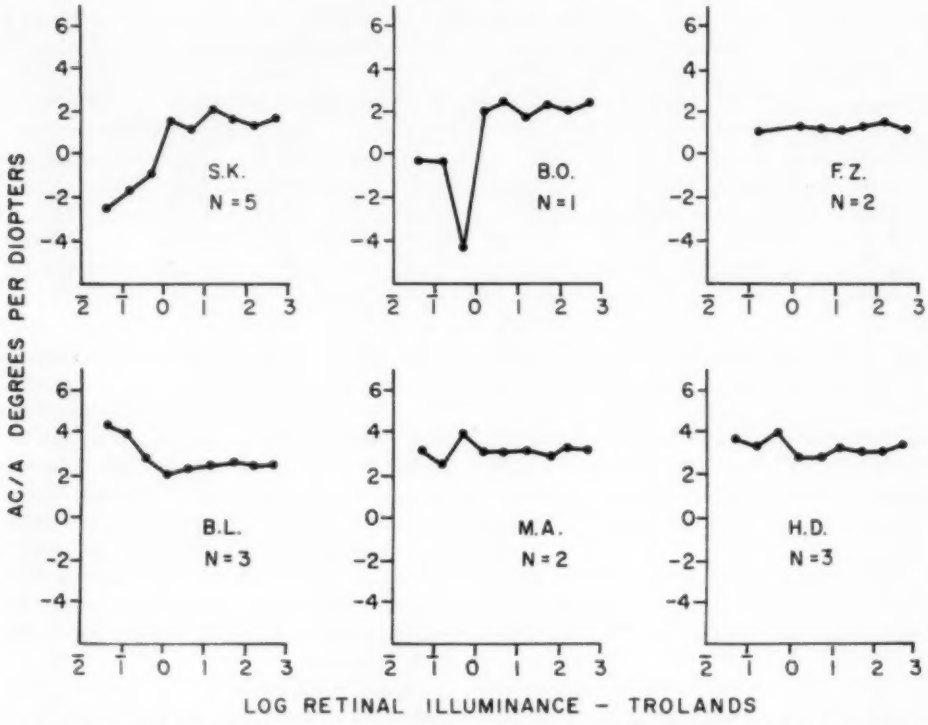

Fig. 3 (Alpern and Larson). The response AC/A as a function of retinal illuminance for each of the six observers studied. The value for N on each graph represents the number of times each experiment was repeated.

that the border line between photopic and scotopic levels of retinal illuminance is somewhere between 1.0 and 0.1 troland[8] it is clear that for each of the six subjects there is no change of AC/A as the retinal illuminance is varied over photopic levels. This is in spite of the fact that the amplitude of accommodation is considerably reduced over this same range. While all of the observers are reasonably consistent in this effect there are individual differences in the changes which occur at scotopic levels. It is apparent that in some subjects the AC/A decreases with further decrease of light level below the photopic threshold, while other subjects show a slight increase. In still others the AC/A remains essentially unchanged even at these extremely low levels. While the reasons for these differences cannot be easily explained it is probable that the rather extensive variability of the accommodation process at these low levels is an important factor.[9] At any rate even in the one or two cases in which the AC/A shows an increase at low scotopic levels, the magnitude of the change is, in each case, quite small. An analysis of variance of the data in this figure shows that while significant differences ($F = 8.02$; 5 d.f.; $p < 0.01$) exist between observers in AC/A the differences in AC/A at different luminance levels are not at all significant ($F = 0.71$; 8 d.f.).

The upper graph of Figure 4 shows the mean change in AC/A with retinal illuminance. On the average there is a slight tendency to decrease in AC/A with luminance in the scotopic range but it has already been emphasized that this difference is not significant.

The lower graph in this same figure shows

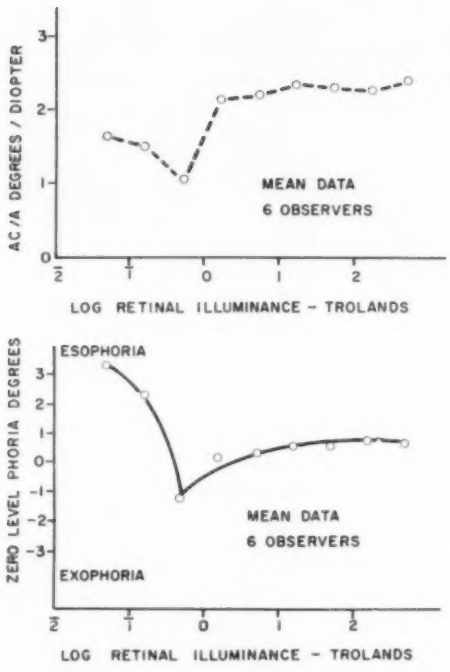

Fig. 4 (Alpern and Larson). Mean data of the six observers in this experiment. The upper figure shows the mean data of Figure 3, that is, the response AC/A as a function of retinal illuminance. The lower graph shows the mean change in the (extrapolated) zero level phoria with luminance.

the average change in zero level phoria with retinal illuminance. Analysis of variance of these latter data shows that—contrary to the result obtained with the AC/A—while significant differences do not exist in zero level phoria between different observers ($F = 0.4$; 5 d.f.) significant differences in zero level phoria do occur with change in retinal illuminance ($F = 2.46$; 8 d.f.; $p < 0.05$). The lower graph in Figure 4 shows that on the average decreasing retinal illuminance at photopic levels is associated with a general trend toward less esophoria; at scotopic levels lowering the light level is associated with a trend toward increasing esophoria.

Discussion

The results of these experiments clearly show that the AC/A does not change significantly with decreasing retinal illuminance even though reducing the light level is associated with marked losses in the amplitude of accommodation. How does this compare to two other conditions in which the amplitude of accommodation is reduced, that is, cycloplegia and age?

When the ciliary muscle is partially paralyzed by the topical application of atropine-like substances, not only does the amplitude of accommodation decrease but the AC/A increases. This result has been obtained by a number of independent investigators using a variety of different techniques.[10-13] Figure 5 illustrates some typical measurements of this kind. The data show the heterophoria measurement obtained for different accommodation values on the haploscope. The unfilled circles represent the data obtained under normal viewing conditions, the AC/A being in this case $2.65 \pm 0.28°$/diopter. When a cycloplegia (five-percent eucatropine and one-percent hydroxamphetamine instilled in two drops, the second 5 minutes

TABLE 3

Effect of luminance on the response AC/A (degrees/diopter)

Log I	S. K. N=5	B. O. N=1	F. Z. N=2	M. A. N=2	H. D. N=3	B. L. N=3	M. N.
2.68	1.68	2.46	1.20	3.25	3.40	2.45	2.41
2.19	1.48	2.04	1.45	3.26	3.07	2.39	2.28
1.68	1.71	2.46	1.28	2.94	3.04	2.49	2.32
1.19	2.14	1.91	1.11	3.21	3.33	2.46	2.36
0.68	1.22	2.54	1.18	3.20	2.85	2.37	2.23
0.19	1.60	2.08	1.32	3.14	2.80	2.05	2.16
$\bar{1}$.68	−0.97	−4.36		4.00	4.00	2.76	1.08
$\bar{1}$.19	−1.69	−0.29	1.16	2.56	3.40	3.93	1.51
$\bar{2}$.68	−2.52	−0.23		3.16	3.67	4.18	1.65

TABLE 4

THE EFFECT OF TARGET LUMINANCE ON HORIZONTAL PHORIA WHEN THE ACCOMMODATION RESPONSE IS ZERO (EXTRAPOLATED)

Log I	S. K. N=5	B. O. N=1	F. Z. N=2	B. L. N=3	H. D. N=3	M. A. N=2	M. N.
2.68	0.30	0.00	0.93	1.37	0.93	0.93	0.74
2.19	0.11	1.24	0.50	1.06	0.66	1.15	0.79
1.68	−0.42	0.02	1.05	0.20	1.64	1.14	0.60
1.19	−1.69	2.37	0.36	1.54	0.62	0.48	0.61
0.68	− .34	−0.05	1.03	1.69	1.18	−1.31	0.37
0.19	−1.58	0.29	0.58	1.74	0.38	−0.16	0.21
I.68	.38	−3.40		0.58	−0.39	−3.06	−1.18
I.19	6.94	2.82	1.55	1.68	−0.37	1.29	+2.32
2.68	8.97	3.05		1.25	−1.74	5.38	+3.38

after the first) was topically applied to the conjunctival sac of the fixing eye and these measurements repeated after the drug had become effective, the data represented by the filled circles were obtained. It is seen that the rate of change of convergence increases markedly to about 28.6°/diopter, that is, an increase of 10.8 times. The explanation for this result is that when a given innervation to the ciliary muscle fails to produce the anticipated change in the refractive power—under the influence of the drug—then greater accommodation innervation is obtained and this increased innervation to the ciliary muscle is characterized by a further increase in accommodation vergence.

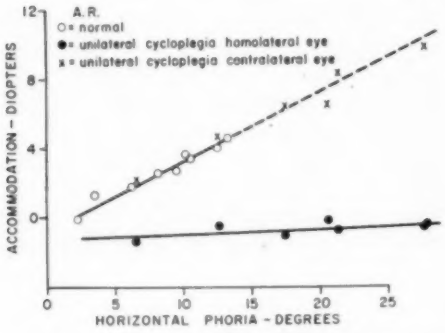

Fig. 5 (Alpern and Larson). The effect of cycloplegia on the relation of vergence and accommodation. The unfilled circles represent data obtained under normal viewing conditions; the filled circles are measurements made about one hour after the instillation of two drops five-percent eucatropine and one-percent hydroxamphetamine into the conjunctival sac of the fixing eye. The crosses represent simultaneous measurements of the contralateral (non-cycloplegic) eye.

In order to prove that this interpretation is correct measurements were made of the changes in accommodation in the eye in which no drug was instilled while its cycloplegic fellow was fixating. These data are illustrated by the x's in the same figure. Because Hering's law of equal innervation to the yoked ocular muscles of the two eyes applies to the ciliary muscle with the same validity that it does to the extraocular muscles, the increased innervation to the ciliary muscle of the cycloplegic fixing eye is associated with a marked increase in refractive power of the noncycloplegic occluded eye. Moreover, the relationship between the amount of convergence and the change in refraction of *this* eye is precisely that obtained under normal viewing conditions.

In contrast to the effect of cycloplegia the reduction of the amplitude of accommodation associated with increased age is not associated with a similar increase in the AC/A. Measurements on a single individual over extended periods of time have not been reported in any detail in the literature. On the other hand, random sampling of the population AC/A at various age levels have been carried out. While these measurements have been made on the stimulus AC/A this probably does not introduce any major error for the age groups of immediate concern for the present purposes. The results of two such studies[14, 15] which are in essential agreement

with analyses reported by others[16,17] are summarized in Figure 6. Alpern and Hirsch summarized the findings on 1,202 normal observers, seven to 47 years of age. All measurements were made through the distance spectacle correction and none of the subjects used additional plus lenses in order to read the fine row of letters in the near (that is, 40 cm.) heterophoria measurements. The stimulus AC/A was estimated by computing the accommodation vergence associated with a change in heterophoria on shift of gaze from far to near. Davis and Jobe made similar calculations on more than 10,000 observers studied with the orthorater.[15] While differences between the two sets of data are apparent these are probably related to differences in the testing procedure. However, for the present purpose the important point to be emphasized is that up to the age of 42 years, when the average amplitude of accommodation is less than five diopters, no increase in AC/A comparable to that obtained under the influence of cycloplegia is apparent. If anything, the stimulus AC/A shows a modest reduction during this time. While the reason for this reduction is not clear it is possible that it is related to the increased depth of field associated with smaller and smaller pupils with increased age. With more depth of field a given accommodation stimulus would evoke progressively smaller accommodation responses and correspondingly larger amounts of exophoria at 40 cm. with increased age.

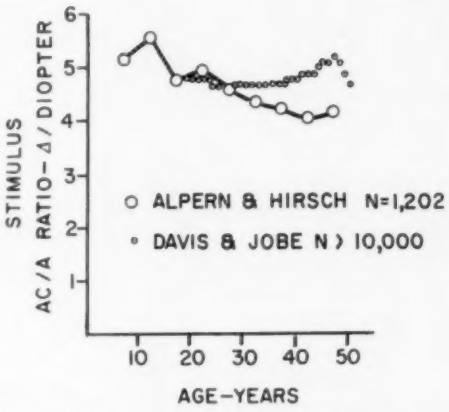

Fig. 6 (Alpern and Larson). The effect of age upon the stimulus AC/A.

A comparison of the effects of the reduction of the amplitude of accommodation with age, cycloplegia and luminance level upon the AC/A is made in Figure 7. The measurements of age are those obtained by Alpern and Hirsch[14] when compared to the mean amplitude of accommodation for the same age group as measured by Duane.[18] The measurements with cycloplegia are some recent measurements of Morgan,[11] a highly practiced observer, on his own eyes. The luminance data are those mean data of the present study (fig. 4) when compared to the reduction of the amplitude of accommodation at the same light level interpolated from the data of Figure 1. The figure clearly

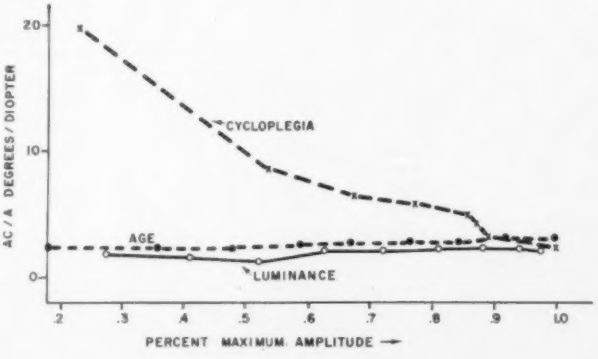

Fig. 7 (Alpern and Larson). A comparison of the effect of reduced amplitude of accommodation upon the AC/A. The crosses are the effect of cycloplegia measured by Morgan with a haploscope on his own eyes.[11] The filled circles represent the effect of age using the data of Alpern and Hirsch[14] of Figure 6 when compared to the reduction of amplitude with age reported by Duane.[18] The unfilled circles show the effects of luminance when the mean data of Figure 4 (upper graph) are compared to the reduced amplitude at the same light level (Figure 1.).

demonstrates that changing luminance just like changing age does not appreciably alter the relation between accommodation and accommodative vergence. Apparently, the reduction in the amplitude of accommodation with luminance (or with age) does not result in a clear increase in innervation to the ciliary muscle in order to focus at near such as one finds with partial cycloplegia (fig. 5). The term "night presbyopia" seems to be a peculiarly well chosen word provided one may use the change in AC/A as a suitable criterion.

On the other hand, one should not press the analogy too far. It is agreed that the major factor in presbyopia is lens sclerosis and the reason that this influences the relation of accommodation and accommodation vergence in the same way that reducing the amount of light reaching the retina is not obvious. Presumably in both increasing age and reduced light level, the deterioration of the amplitude of accommodation does not elicit any increased ciliary innervation in order to produce a unit change in the form of the lens. In the case of reduced light level, this is true even though the ability of a unit change of the stimulus to evoke an accommodation response gradually deteriorates along with the amplitude. Why the situation should be otherwise in the case of partial cycloplegia is not apparent from the available data.

Finally a word should be said as to the change in zero level phoria which occurs with reduced light level. The zero level phoria measurement is an indication of the amount of tonic convergence. Ivanoff[19] has reported that the binocular convergent position of the eyes (as measured by a fixation disparity procedure) is generally more convergent as the light level is reduced. The present results indicate that when the level of light is below photopic levels some of this increased convergence may be due to increased tonic convergence. How much of the total effect obtained by Ivanoff can be attributed to this effect on tonic convergence can only be decided after ways have been obtained for measuring the relation between phoria and accommodation at much lower light levels than any so far employed.

Summary

Haploscopic measurements of the AC/A on six prepresbyopic adult males at various levels of retinal illuminance have been employed to demonstrate the fact that the reduction of the amplitude of accommodation with light level is not associated with a corresponding change in AC/A. In this respect the reduction of the amplitude with reduced light level is more closely similar to the reduced amplitude with increasing age than it is to the reduced amplitude of partial cycloplegia. Tonic convergence, on the other hand, tends to decrease with reduction of light level in photopic vision but to increase with further reduction of light level at scotopic levels.

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Discussion

Dr. R. H. Peckham (Bethesda, Maryland): In the averaging of the six subjects, some of whom had one trial and others five trials, was there any weighting of the number of trials in setting up that average?

Dr. Alpern: We gave each subject, rather than each trial equal weight. This seems to be the preferred procedure since AC/A is quite constant in any given individual but varies rather markedly from one subject to the next.

Dr. Romaine: Were these patients tested for dark adaptation beforehand?

Dr. Alpern: Not as a special control in this particular experiment. However, you must keep in mind that we work in our own laboratory on one another to a considerable extent, and in the process we have obtained in the course of several years, dark adaptation studies on virtually all of the observers who were used. We have no evidence in any of the observers whom we have studied that there was any defect of this sort.

FLUORESCEIN IN APPLANATION TONOMETRY*

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Introduction

Some confusion seems to have arisen regarding the use of fluorescein in applanation tonometry.[1] The difficulty hinges on a lack of distinction between the concentration of fluorescein in the tears, and the volume of tears forming the meniscus between applanation prism and cornea. Goldmann and Schmidt in their classic paper on applanation tonometry[2] present tables which show that if there is a large excess of fluid in the meniscus which forms between cornea and flattening surface, the curvature pressure of the meniscus surface film is reduced. In this case the measured pressure may be as much as 2.0 mm. Hg too high. They did not discuss the concentration of fluorescein in the tear film. However, they did state that in their method: "5% fluorescein solution is dried on a paper strip 5 mm. wide. Such a dry strip is placed in the conjunctival sac briefly."

The purpose of the fluorescein in the

* From the Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine. The research relating to this study was financed in part under a grant to Washington University School of Medicine made by the Alfred P. Sloan Foundation Inc. The grant was made upon recommendation of the Council for Research in Glaucoma and Allied Diseases. Neither the Foundation nor the Council assumes any responsibility for the published findings in this study.

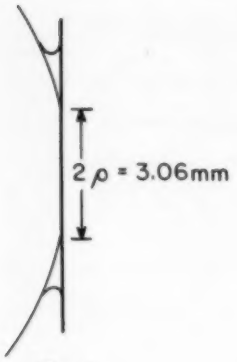


Fig. 1a

Fig. 1b

Fig. 1 (Moses). (a) Schematic cross-section of contact between cornea and applanation prism. (b) Cross-section of the meniscus of tear fluid. The dots represent fluorescein molecules.

tears is to delineate the margin of the applanated area. The relationship of the cornea, the flattening surface, and the fluorescein-stained tear film is given in cross section in Figure 1-a. The flattened area (2ρ) is taken to be that region inside the meniscus ring where fluorescence is not seen. In measuring the diameter of this area it is assumed that the wedge of stained tear fluid is visible to its apex. It is this unqualified assumption that is questioned in the present paper. Certainly, unstained meniscus fluid cannot be differentiated from cornea during use of the tonometer. A brief consideration of Figure 1-b points up the question. If the dots are fluorescein molecules evenly distributed in the tear fluid there are fewer in the apex of the wedge than in the base. Therefore one expects the fluorescence of the apex to be less bright than that of the base. If the apex is sufficiently dim it will be missed entirely. In this circumstance the measurement will be made as in Figure 2, from the inner edge of the visible fluorescense, while the cornea is flattened to a lesser degree. If this happens, one may expect the measurement to represent an underestimate of pressure.

The important questions are: (1) Can such an underestimate occur, (2) of what magnitude may it be, (3) what conditions enhance the error, and (4) how can such underestimate of pressure be reduced?

Methods

Fluorescein solutions of various concentrations were prepared by diluting stock 2.0-percent fluorescein (Ophthalmos) with normal saline, 0.2-percent Novesine (Wander), 0.5-percent Ophthaine (Squibb), and anesthetic solution plus saline or buffer. A lucite ball (diameter 25 mm.) was held by a clamp to the headrest of the Haag-Streit slitlamp-microscope (unimproved model). The applanation tonometer prism was held against the ball with a force of 1.0 gm. A drop of fluorescein solution was placed between ball and prism, and the resulting pattern was viewed at ×9.5 magnification, the light switch being in the position for normal use. The angle between slitlamp and microscope was constant at 65 degrees. The tonometer prism was decentered upward slightly so that the contact area was seen as a circle through the lower prism. The diameter of the area of no visible fluorescence was measured with an eyepiece reticule (fig. 3).

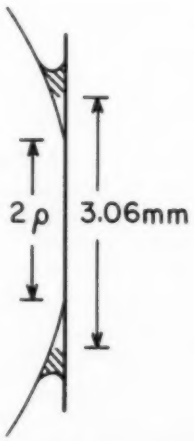


Fig. 2 (Moses). If the fluorescein concentration in the tears is low the apex of the meniscus is invisible, and the actual contact between prism and cornea (2ρ) is less than the apparent contact.

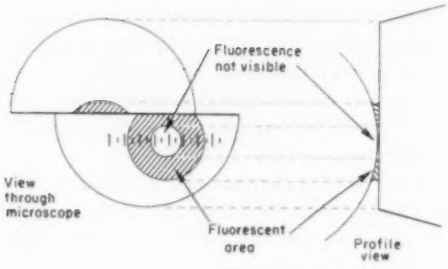


Fig. 3 (Moses). The plastic ball test device as seen through the microscope and in cross-section (see text).

From the diameter of the nonfluorescent spot and the radius of the plastic sphere the thickness of fluorescent meniscus minimally visible is easily calculated (fig. 4*).

In calculation of the clinical measuring error, the measured radius of applanation = radius of flattened cornea + width of invisible apex of meniscus. If the concentration of fluorescein in the tear fluid is known, then the minimal visible thickness of film is known from the work with the plastic ball and the actual radius of applanation may be calculated (fig. 5†).

When the radius of the flattened area is not that for which the instrument was designed, the scale $\times 10$ no longer may be interpreted in mm. Hg, but the scale reading (gm.) must be multiplied by a factor appropriate to the actual radius of applanation.

$$\left(\text{Pressure} = \text{Force}\ \frac{1}{1.36\pi\ (\text{radius of applan.})^2}\right),$$

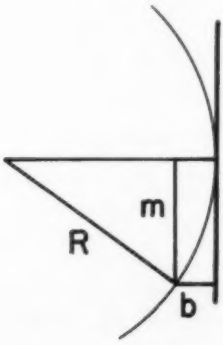
where pressure is in mm. Hg, force is in grams, and radius is in mm.)

Furthermore, Goldmann and Schmidt have shown that for applanation diameters of less than three mm. the elasticity of the cornea and the surface tension effect of the meniscus no longer balance, the meniscus force being the greater. This is a second source of underestimate of intraocular pressure. The error due to imbalance of corneal and meniscus forces at reduced applanation diameters may be estimated from Figure 6 modified from Goldmann and Schmidt.

In order to provide standards for the measurement of the concentration of fluorescein in the tears, strips of filter paper

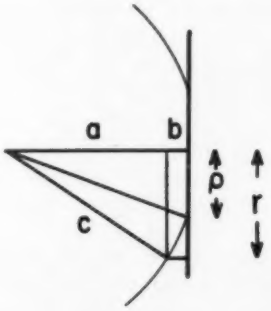
* (Fig. 4) b = thickness of film
m = radius of nonfluorescent area
R = radius of plastic sphere

$$R^2 = m^2 + (R-b)^2$$
$$b = R - \sqrt{R^2 - m^2}$$



† (Fig. 5) c = radius of curvature of cornea
b = thickness of fluid
r = apparent radius of applanted area $\left(= \frac{3.06}{2}\ \text{mm}\right)$
ρ = actual radius of applanation

$$c^2 = (a+b)^2 + \rho^2$$
$$a = \sqrt{c^2 - r^2}$$
$$c^2 = (\sqrt{c^2 - r^2} + b)^2 + \rho^2$$
$$= \sqrt{c^2 - (\sqrt{c^2 - r^2} + b)^2}$$



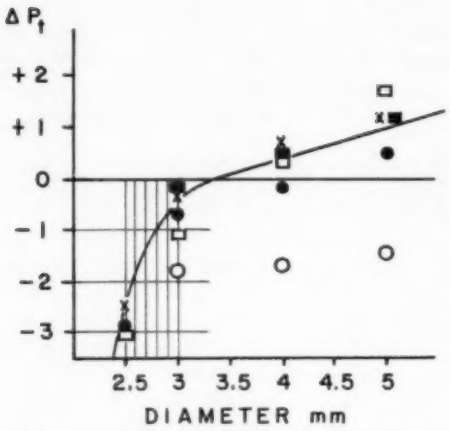


Fig. 6 (Moses). The difference between calculated and actual intraocular pressure for different diameters of applanation (after Goldmann and Schmidt).

were dipped into solutions of known concentration and allowed to dry. An unstained paper strip was touched to the conjunctiva of the lower lid of the eye in which fluorescein had been instilled. This strip, when dry was compared to the standards. Color matching proved to be very easily done.

pH of the tears which was measured with pHydrion indicator paper was estimated immediately.

Results

The thickness of minimally visible fluorescein solution at varying concentrations was measured for stock 2.0-percent fluorescein diluted with (a) normal saline, (b) equal parts of normal saline and Novesine (c) Novesine, (d) equal parts of normal saline and Ophthaine, (e) Ophthaine, and (f) seven parts phosphate buffer (pH 7) and one part Ophthaine. The results are presented in Figure 7. It is apparent that at low fluorescein concentrations the fluid layer must be increasingly thick for the fluorescense to be visible. It is also clear that fluorescein dissolved in topical anesthetic is much less fluorescent than in saline.

The error in measurement of pressure at different fluorescein concentrations is calculated from the above considerations as error due to overestimate of applanated area plus error due to imbalance of corneal and meniscus forces. The correct pressures are given in Figure 8 for an assumed apparent intraocular pressure of 15.5 mm. Hg.

That low fluorescein concentrations in the tears may actually occur has been demonstrated by the filter paper comparison method. Measurements made immediately following routine tonometry gave concentrations varying from 0.25 to 0.008-percent fluorescein. It is seen from Figure 8 that the lower concentration may introduce a sizeable underestimate of pressure.

It is also apparent from Figure 8 that the topical anesthetic solutions Novesine and Ophthaine quench the fluorescence of fluorescein, and that the greater the concentration of anesthetic in the solvent, the greater the quenching. It is well known that fluorescein loses its ability to fluoresce in acid solutions[3] and both anesthetics are acid (Novesine pH 4, Ophthaine pH 4.5). Commercial fluorescein paper* moistened with distilled water is also acid (pH 4.5). However, the fluorescence of anesthetic solutions of fluorescein is only slightly restored by neutralizing the solution, so the anesthetic base must also quench the fluorescence to some degree (fig. 8). Thus, even though the conjunctival sac after preparation for tonometry with Ophthaine and fluorescein dissolved in Ophthaine (Fluor-I-Strip moistened with Ophthaine) is pH 6.5 (normal pH 7.0), one may be sure that the fluorescence is not so bright as if a non-quenching fluorescein diluent were used.

Discussion

Measurement of intraocular pressure with the Goldmann applanation tonometer requires that the meniscus of tear fluid surrounding the flattened corneal surface be sufficiently stained with fluorescein in a fluorescent state so that the very apex of the wedge-

* Fluor-I-Strip (Ophthalmos).

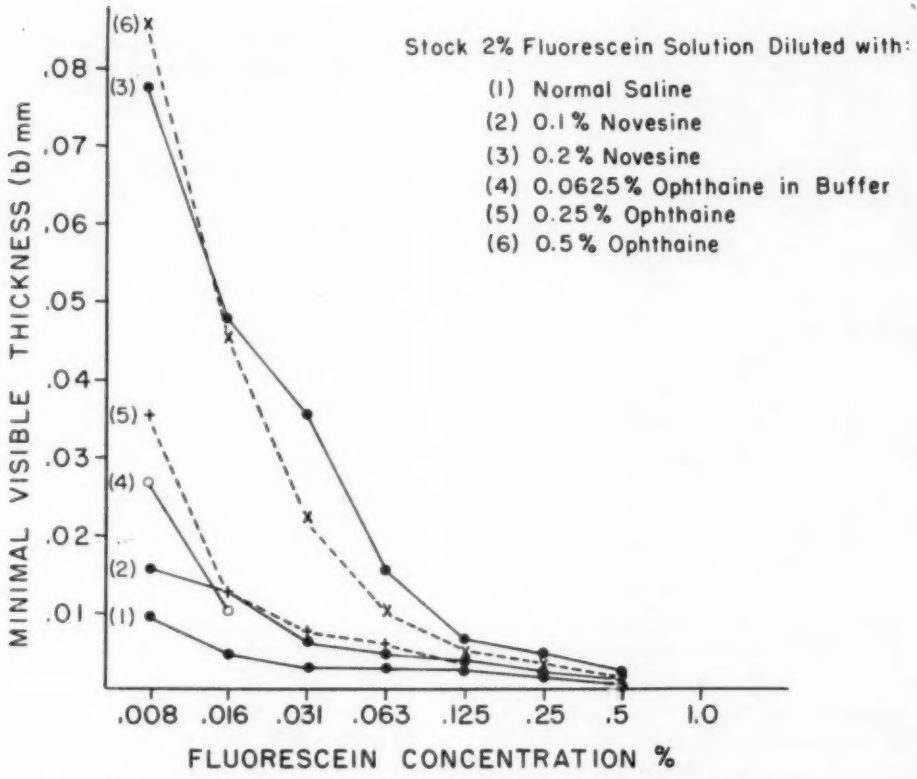


Fig. 7 (Moses). The thickness of fluid minimally visible as fluorescent for different fluorescein concentrations and solvents.

shaped meniscus is visible. If the apex of the wedge is not visible, a thicker layer of fluid which is visible will be judged as the apex, and the apparent flattened area will consist of a smaller than standard flattened surface of cornea plus a rim of invisible tear fluid.

The thickness of a wedge of fluorescein-containing fluid minimally visible as fluorescent is inversely proportional to the concentration of fluorescein and directly proportional to the concentration of substances which suppress the fluorescence. That is, with a high concentration of fluorescein (up 1.0 percent; 2.0 percent is not visibly fluorescent under the test conditions) and a low concentration of quenching substance (anesthetic solution) one obtains maximal fluorescence and minimal invisible wedge apex. With highly dilute fluorescein and the presence of quenching substance much of the meniscus apex will be mistaken for flattened cornea and the force with which the applanation prism is pressed against the eye will be less than that required to flatten a standard area of cornea. This will result in an underestimate of pressure. Moreover, the surface tension of the tear fluid pulling the prism toward the eye is greater than the force of elastic deformation of the cornea at applanations less than standard, and an additional underestimate of pressure is introduced.

That an appreciable underestimate of pressure can actually result in clinical practice from the error under discussion is shown by the results of the study which

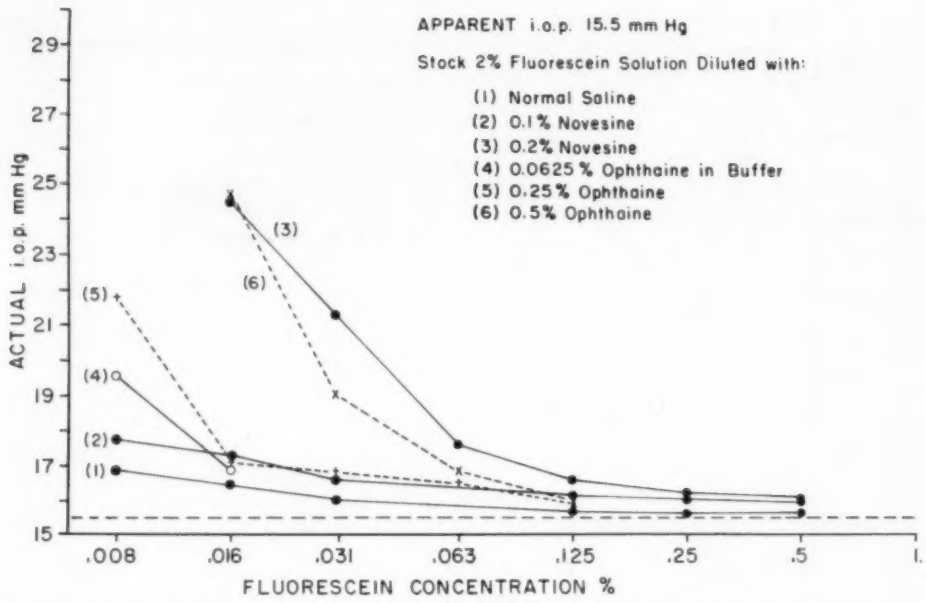


Fig. 8 (Moses). The findings shown in Figure 7 have been translated in terms of actual intraocular pressure if the apparent intraocular pressure as judged by the scale reading is 15.5 mm. Hg.

stimulated this report: a worker measured the intraocular pressure of 40 normal subjects and found an average of 14.1 mm. Hg. This proved to be significantly different from Goldmann and Schmidt's average of 15.45 mm. Hg at the 0.001 level. An observation of his technic revealed that he placed a dry strip of fluorescein paper in the lower cul-de-sac for no more than one second. The tear fluid was obviously understained.

A similar potential error results from moistening the fluorescein paper with topical anesthetic. Even though by this method a high concentration of fluorescein in the tears is obtained, it may be expected that much of it will be in a nonfluorescent condition due to the excess of anesthetic solution.

Conclusions

In applanation tonometry an insufficient concentration of fluorescein in the tear fluid will produce an underestimate of intraocular pressure.

The two topical anesthetic solutions tested quench much of the fluorescence of fluorescein and tend to produce thereby an underestimate of intraocular pressure.

It is suggested that in order to avoid such an underestimate, after topical anesthesia, fluorescein paper be moistened with saline or distilled water and applied to the conjunctiva so that a liberal quantity of fluorescein in a fluorescent condition will be present in the tear fluid during tonometry.

640 South Kingshighway (10).

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Discussion

Dr. Langham: I enjoyed hearing Dr. Moses' presentation very much, and he has brought up a very important point that I would like to support.

The fluorescence of fluorescein is maximal and constant between pH 7.0 and 8.0, however, as soon as the pH falls silghtly below pH 7.0, the fluorescence decreases very sharply indeed, therefore if an anaesthetic having buffering action and an acid pH is used, fluorescence of the fluorescein solution will be diminished. To avoid this, I have been using fluorescein dissolved in a phosphate buffer of pH 7.4.

Dr. Moses also brought out the point that fluorescence diminishes again as the concentration of fluorescein rises above a certain level. We have found that the fluorescence of the fluorescein solution increases proportionately with the concentrations up to approximately 0.3 mg. percent.

Dr. Moses: The concentrations that you find as maximally fluorescent are much lower than the concentrations I have been talking about as clinically useful. I wonder if you are talking about the yield of fluorescence. I am speaking of the visibility, which is not directly related to the yield.

Dr. Langham: Although it is very true that they can't be directly compared as there is a great dilution factor when you apply a drop of fluorescein to the eye.

Dr. Moses: Yes; above one percent you do tend to lose fluorescence. If you put too much fluorescein in the eye when you put the prism against the cornea and see nothing but brown rings, take the prism away for a moment and ask the patient to blink, this will dilute the fluorescein to the fluorescent level.

Dr. Roberts: Dr. Moses, this point of the breadth of the meniscus was at least to a minor degree emphasized by Drs. Goldmann and Schmidt in their verbal comments about the use of this instrument, and they have urged that you not get an excessively broad meniscus, which is essentially a function of too much tears rather than too much fluorescence.

I am a little at a loss as to why it should affect your reading, if it does. Do you think it does?

Dr. Moses: Yes, it does; but you have to go to quite a broad meniscus to do this. If you have a small meniscus it has a highly curved surface which exerts a considerable curvature pressure. As the meniscus gets broader, the curvature of the surface is less, and it exerts a lower curvature pressure. This pressure is toward the eye; therefore, when the pressure is reduced you have to exert more force with your spring balance, and therefore you get an overestimate of pressure with a too-broad meniscus.

Dr. Roberts: Clinically, however, do you feel that it has to be an excessively broad meniscus to be of importance?

Dr. Moses: Yes. Sometimes when you are measuring, a drop of tears runs down from the patient's upper lid to the prism. You get a very large increase in fluid, and you can measure the difference in apparent pressure of perhaps 1 mm. of mercury. It has to be a really broad meniscus.

On the other hand, I think some workers, in attempting to get a narrow meniscus have almost deliberately used too little fluorescein. This allows you to see only the heel of the wedge, and so they say to themselves, "I have a nice narrow meniscus, and this is what Goldmann and Schmidt were talking about." That is not true at all. They weren't talking about that. So, you are only kidding yourself when you see a hairline meniscus.

THE PROGRESSIVE CHANGES IN THE PATHOLOGY OF EARLY RETROLENTAL FIBROPLASIA

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Boston, Massachusetts

Usually one gives a paper to present some interesting new facts. In this case that is partially so. The actual pathologic sections are unusual as they are examples of early changes of retrolental fibroplasia. As the disease is not a fatal one, specimens of its early stages are rare and hard to come by. In fact the Foundation for Vision which grew out of Terry's[1] original work has only two of these specimens. An excellent description of the pathology has already been given by Friedenwald, Owens and Owens,[2] Heath,[3] and in *Ophthalmic Pathology*.[4]

Actually these slides do not differ a great deal from those already mentioned. However, I hope to accomplish two things: (1) to correlate the disease as seen clinically with the pathologic findings; (2) to present these sections so that you can visualize the different stages as the disease progresses, leading to the destruction of the eye. Early the changes are reversible, later irreversible.

Lastly, with the discovery of oxygen as the leading etiologic factor, the incidence has markedly decreased. Patz's[5,6] work confirmed the importance of oxygen as an agent,

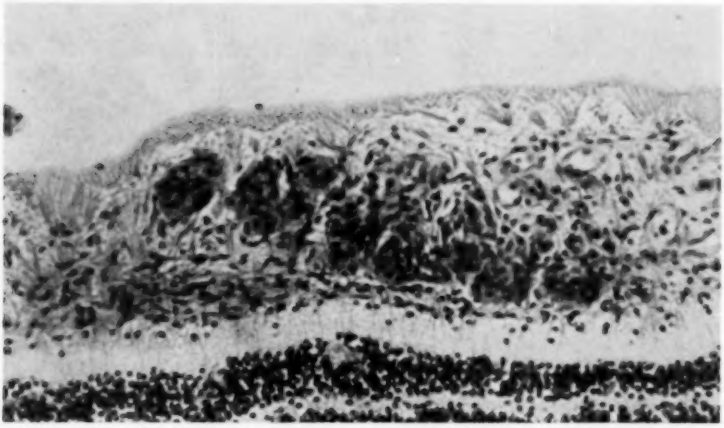

Fig. 1 (Chisholm). Multiple whorl-like nests of endothelial cells proliferating in nerve-fiber layer, resembling glomerular tufts.

as well as its ability to produce lesions in mice, rats, kittens, dogs, and so forth which are quite typical of retrolental fibroplasia. Naturally as the disease was controlled, interest in it has all but vanished. However, as the true etiology is unknown, sporadic cases without oxygen or in term babies still appear. Also, cases are seen from time to time in babies from smaller hospitals where the oxygen has not been controlled or measured accurately.

Case reports

Case 1

Baby F., born October 31, 1949, birth weight two lb. two oz. On December 5, 1949, right inferior temporal vein ×2; left superior temporal vein ×3. On January 26, 1950, aged eight weeks, last seen, (died shortly thereafter). Vascular picture same but more tortuous. Right eye: localized separation from inferior temporal vein up to the 10-o'clock position. Left eye: inferior temporal separation. Classified: active stage 3. Pathology examination left eye: marked neovascular formative tissue on the surface of the retina. Retina in multiple folds in region of ora. Newly formed fibrous vascular strands in anterior vitreous.

Case 2

Baby D., born December 5, 1950, birth weight four lb. First examined January 15, 1951. Veins ×3. Arteries so tortuous like caput medusa. Retinal hemorrhages one week later and areas of whitish edema under retina. On February 8th left eye: membrane forming in posterior vitreous. On February 11th, area neovascularization right eye temporally. On February 25th, right eye: membrane growing. Left eye: early dragging of disc. Last seen March 8th (13 weeks). Left eye: membrane and retinal fold extending down from the 12-o'clock position covering lateral half disc and extending on down. Classified: stage 3 cicatrical left. Died suddenly March 8th.

A section showing the early changes of dilated blood vessels in the nerve fiber layer of the retina, because of its simplicity, is not included. In Figure 1 the whorl-like nests of proliferating endothelial cells in the nerve fiber layer represents the earliest changes of neovascularization. In Figure 2 buds from these nests are becoming canalized to form new blood vessels.

Figure 3 shows a blood vessel breaking through the internal limiting membrane into the vitreous. Many capillaries are budding from it. Figure 4 is a later stage now showing some neovascularization on the retina and in the vitreous.

In Figure 5 early neovascularization of the vitreous is taking place at the ora. Figure 6 shows a much more extensive process in the vitreous.

In Figure 7 there is an extensive neovascularization on the surface of the retina. As it is beginning to contract, early retinal folds are being formed. Their apices are being pulled together by the new blood vessels. In

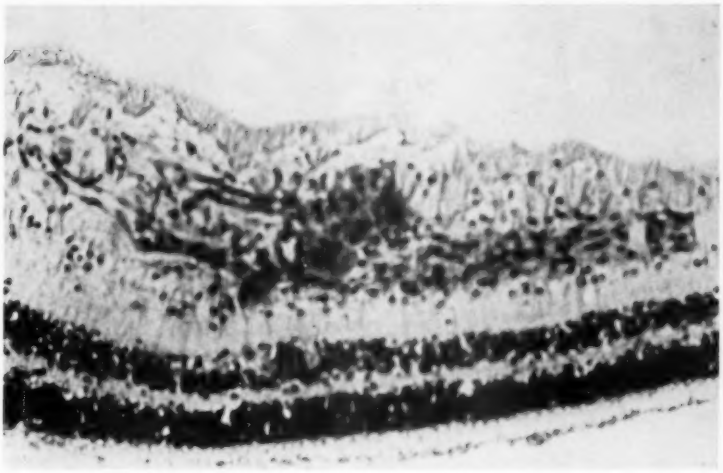

Fig. 2 (Chisholm). Budding from nest of endothelial cells, with canalization resulting in new vessel formation.

Figure 8 an older, well-organized neovascularization tissue is pulling up an area of retina into a fold.

Lastly, Figure 9 shows that the result of traction on the optic nerve from contracture of neovascularization, scar tissue, and so forth is a "dragged disc"—usually temporally. The disc is enlarged, atrophic with the retinal vessels displaced in the general direction of the traction. As this happens a pigment cuff appears on the side of the disc away from the point of traction. In like

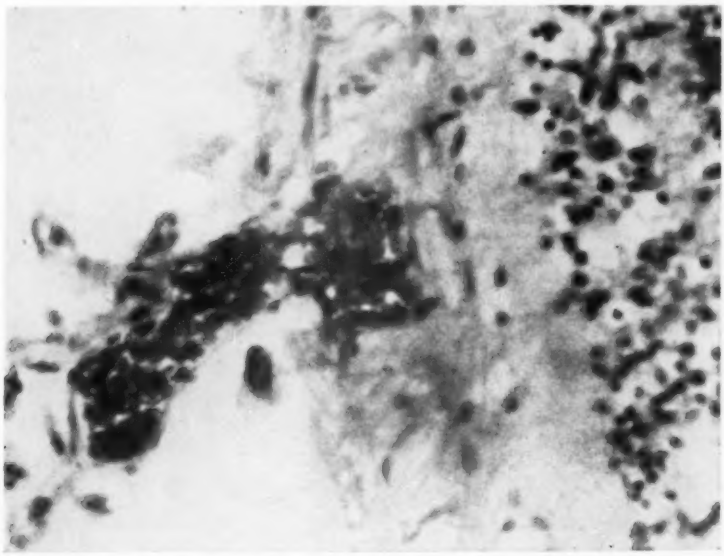

Fig. 3 (Chisholm). Large vessel entering vitreous with many capillary buds.

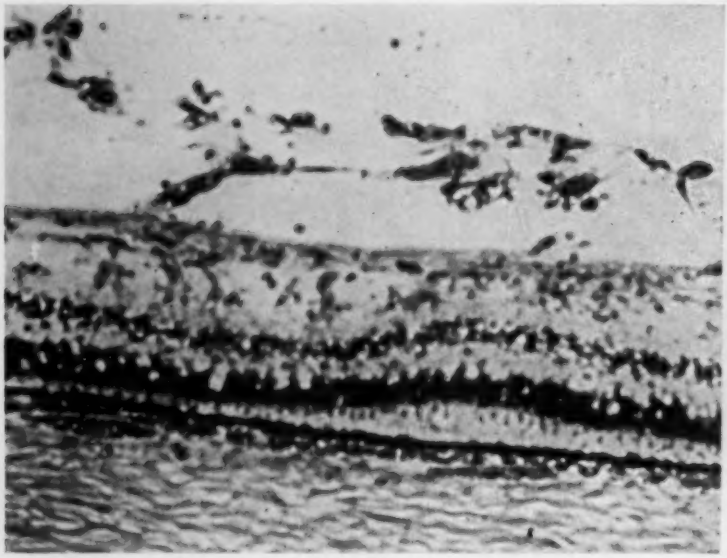

Fig. 4 (Chisholm). Capillary entering vitreous; extensive neovascularization on the surface of the retina

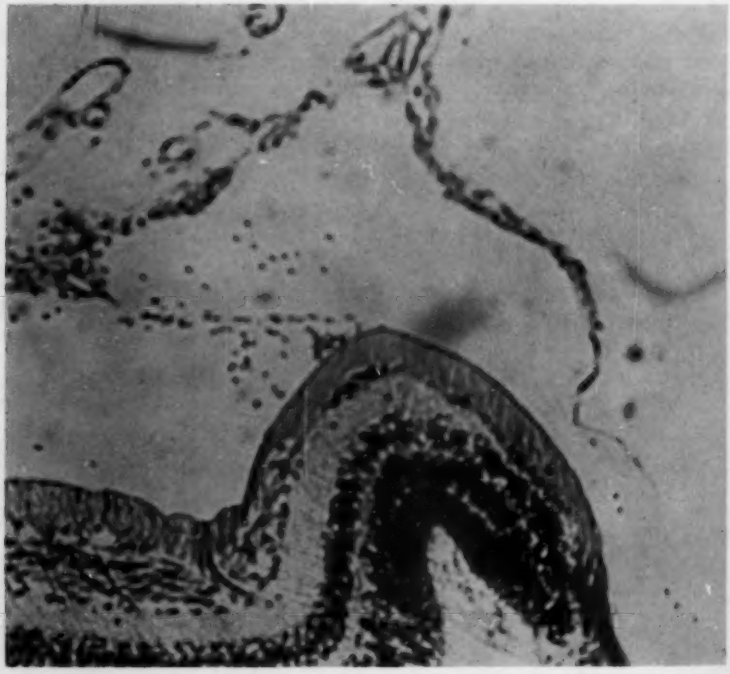

Fig. 5 (Chisholm). Early neovascularization of vitreous at ora.

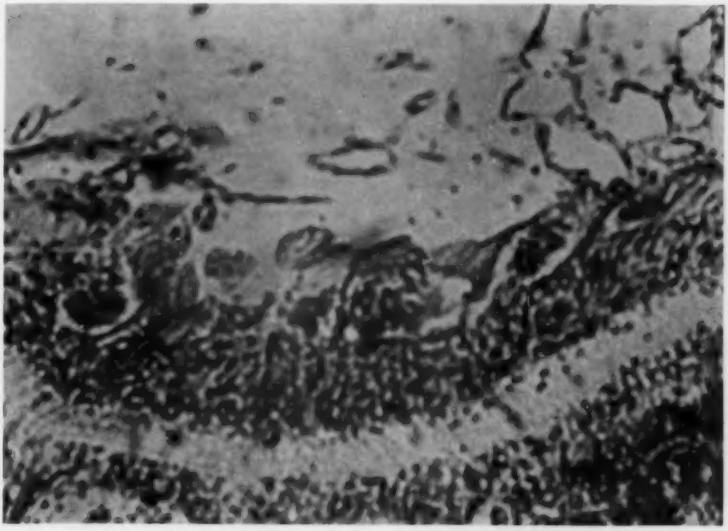

Fig. 6 (Chisholm). Extensive neovascularization of vitreous.

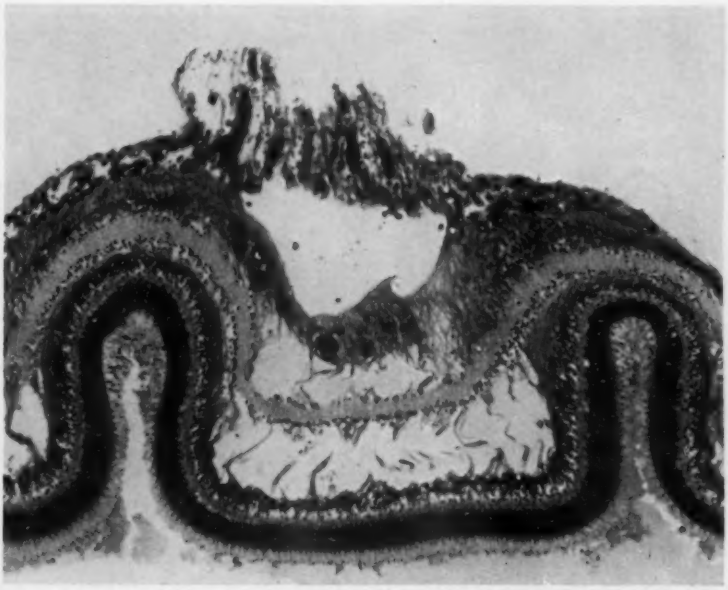

Fig. 7 (Chisholm). Extensive neovascularization on retinal surface. Centrally the multiple new blood vessels are pulling the apices of two folds together.

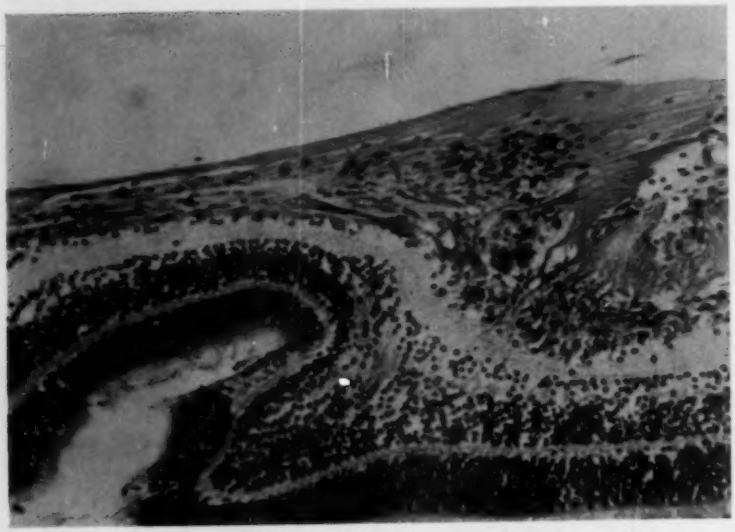

Fig. 8 (Chisholm). Older process. Neovascularization contracting giving a fold from traction.

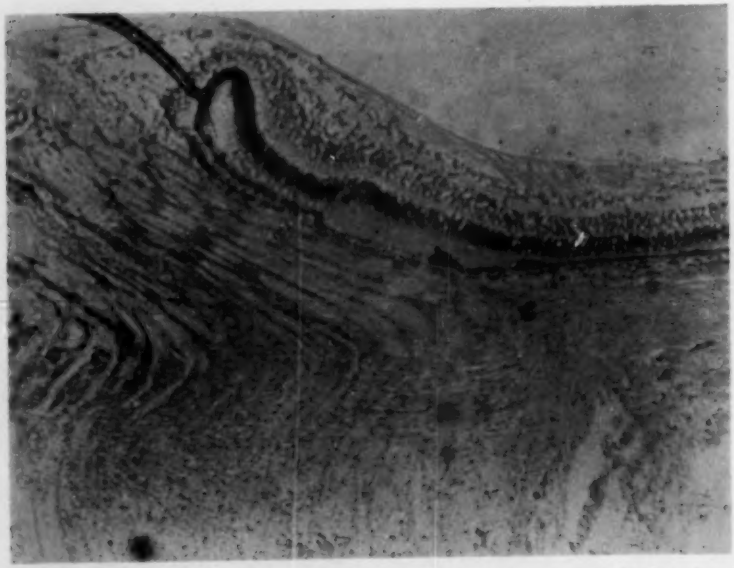

Fig. 9 (Chisholm). Another result of traction from contraction of neovascularization as well as a fo is a "dragged" disc. This section shows the tear in the retinal pigment layer and early proliferation forming the pigment cuff on the side away from the point of traction. Chisholm.[7]

manner, damage to the macula results in eccentric fixation, poor vision, and so forth.

Perhaps I am overapprehensive but I have the feeling that the diagnosis of retrolental fibroplasia is being used all too freely. All retinal lesions in babies are not retrolental fibroplasia. Yet this diagnosis is being made frequently and the baby with such a diagnosis is really headed for trouble. With no known treatment, he receives some palliative care. Often he does not receive even a careful work-up. His doctor, satisfied with the diagnosis, no longer worries over the case. Ophthalmology is going backward in these cases, unknowingly. The following cases explain what I am referring to.

CASE 3

M. N., birth weight five lb. at the age of three and one-half months, brought in because eyes weren't focusing. No oxygen. At examination anterior chamber and tension were normal. Pupils reacted. The pupils were dilated and examination showed a temporal membrane over the ciliary body and elongated ciliary processes. Fold from discs running temporally. Vacuoles in posterior cortex nasally, right. Diagnosis: bilateral retrolental fibroplasia stage 3, cicatrical—in spite of vacuoles in the right lens. Three months later possibility of toxoplasmosis suggested. X-ray studies showed multiple calcified deposits. Pediatric examination microencephalus and positive skin test. The child has become blind and is feeble minded. There is a complete membrane and secondary glaucoma.

CASE 4

H. R. A., Jr., Birth weight seven lb. Mother noted then or next day a whitish reflex in the right eye. Examination showed tension soft, both eyes. Right eye: pupil widely dilated, fixed, and irregular. Large ectropion uveae. Flashlight: irregular, multiglobular yellowish mass filling the nasal half of the vitreous extending almost to the lens. Some small hemorrhage on the surface. Transillumination impaired over the mass. Elongated ciliary processes. Vitreous cloudy, no fundus details. Left eye, dilated, resembles very much the appearance of the right eye. Diagnosis: (1) bilateral retinoblastoma, (2) uveitis (3) intraocular hemorrhage, (4) do not think this is retrolental fibroplasia—as it was present at birth.

Consultation 1. Large organized clot in the vitreous with extensive retinitis proliferans and probably detachment of the retina, certainly in the right eye. I believe this is one of the various types of retrolental fibroplasia, although not the usual one, which shows its growth chiefly after birth in premature infants. Retinoblastoma cannot be excluded.

Consultation 2. Example of massive separation of the retina by hemorrhage. Distinct possibility of retinoblastoma.

Consultation 3. A type of retrolental fibroplasia. The child has become totally blind.

CASE 5

R. W., older brother of patient in Case 6, aged 11 years, birth weight, eight or nine lb., nine ounces. No oxygen. After ether examination, parents were told it was retrolental fibroplasia. Now right globe shrunken, band keratitis. Temporal half of the iris adherent to the cornea. Left eye: band keratitis. Cornea slightly grayish. Deep anterior chamber centrally, with irregular yellow mass in the pupil. Little loss of orbital fat, both eyes. Two sisters born between patients in Case 5 and Case 6 have normal eyes.

CASE 6

E. W., birth weight eight lb., 13 oz. No oxygen. Seen at the age of four weeks, April 17, 1958, because retrolental fibroplasia was suspected and right cornea seemed slightly larger than left. Right pupil four mm. and sluggish. Left pupil active with a yellowish mass behind it. Dilated both eyes. Right eye: large dense mass in vitreous anteriorly and temporally. Strands and mass of tissue over disc with blood vessels on it. Left eye: many vacuoles in posterior cortex: many dense strands anterior, vitreouslike rays then central membrane with hemorrhage on it. Diagnosis: massive vitreous hemorrhage with question of secondary separation. Definitely not retrolental fibroplasia.

On May 29th, complete examination at Children's Hospital negative. Tuberculin test not done. Later examination negative.

On August 2nd, tension of the right eye was increased. Mild buphthalmos. On March 5, 1959, right cornea 14 mm.; left nine mm. Right: peripheral anterior synechia. Iris bends back and is adherent centrally to cataractous lens. Left: pupil widely dilated, advanced cataract, partially calcified.

On October 6, 1959, the peripheral rim of the iris of the left eye was visible. Massive exudate completely filled the angle. No light perception, both eyes.

CONCLUSION

Although retrolental fibroplasia is moderately well controlled, neither its true etiology nor treatment is known. Further research on it is definitely indicated. With the interest revived, doctors would make greater efforts to diagnose the disease correctly. Other obscure retinal vascular lesions would then be recognized, leading to their correct diagnosis and treatment.

330 Dartmouth Street (16).

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THE CLINICAL EVALUATION OF ECHOTHIOPHATE (PHOSPHOLINE IODIDE) IN THE TREATMENT OF GLAUCOMA*

LEON FOWLER GRAY, M.D., AND JOHN P. ROBINSON, M.D.
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The search for more potent and less irritating anticholinesterase agents for the control of intraocular pressure has been going on for many years. In 1875, Laqueur employed physostigmine (eserine) the alkaloid obtained from the calabar bean in the treatment of glaucoma. Ever since this initial discovery a variety of agents have been tried (see table 1). Neostigmine, ortho-neostigmine, and para-neostigmine are the short-acting reversible agents. The other group of agents in this category and the longer-acting relatively irreversible agents include TEPP (tetraethylpyrophosphate), TIPP (tetraisopropylpyrophosphate), HEPP (hexaethylpyrophosphate), mintacol, parathion, and DFP (isoflurophate) or Floropryl. Of all these agents only Eserine, Prostigmin, and Floropryl have stood the test of time as effective agents in the management of glaucoma. Floropryl is considered the most potent of these agents.

In June, 1959, we received Phospholine Iodide for this study. This agent became available early in 1956. Phospholine Iodide is a long-acting miotic agent which is a potent and relatively irreversible inhibitor of acetylcholinesterase. Pharmacologically the action of this drug is like acetylcholine, differing only in its longer duration of activity. The chemical structure of this agent is derived partly from acetylcholine and partly from the phosphate esters. It has the formula you see in Table 2. This compound occurs as a white crystalline solid which is soluble in water. It is stable over a long period of time in its crystalline state; however, when placed in solution it is stable for one month at room

TABLE 1

AGENTS USED TO TREAT GLAUCOMA

Short-Acting Reversible Agents	Long-Acting Relatively Irreversible Agents
Neostigmine	Tetraethylpyrophosphate TEPP
o-Neostigmine	Tetraisopropylpyrophosphate TIPP
p-Neostigmine	Hexaethylpyrophosphate HEPP
	Mintacol (p-nitrophenyldiethylphosphate)
	Parathion (o,o-diethyl-o-p-nitrophenylthiophosphate)
	Isoflurophate DFP (Floropryl)

* From the Department of Ophthalmology, Confederate Memorial Medical Center. Phospholine Iodide, supplied by Campbell Pharmaceuticals, Inc., 121 East 24th Street, New York 10.

TABLE 2

FORMULA OF ECHOTHIOPHATE

Phospholine Iodide	217 MI	Echothiophate Iodide
	+ −	
C_2H_5O	O	
	P—S—$CH_2CH_2N(CH_3)3$, I	
C_2H_5O		

Antidote—Atropine, or its derivatives
Protopam (2 PAM, pralidoxime)

temperature and only six months if kept in the refrigerator.

In the normal human eye the miotic effect of this agent comes on in about 30 minutes and its effect may last for several days. During this time the intraocular pressure is reduced and the aqueous outflow facility is greatly increased. Although the agent, after prolonged use as eyedrops, may be absorbed into the blood stream systemic affects are very rare. When systemic symptoms occur such as persistent diarrhea, profuse sweating or muscular weakness, the drug should be discontinued and the patient treated with atropine or protopam (2-PAM).

The indications for the use of Phospholine Iodide are the same as for the use of other miotic agents. It may be used in chronic open-angle glaucoma and secondary glaucoma of various etiologies and especially aphakic glaucoma. It may also be used in angle-closure glaucoma, with caution, where surgery has been refused or for some reason is contraindicated (table 3).

DOSAGE AND ADMINISTRATION

Due to the potency of this drug it may be used in strengths of 0.06 percent (1/16 percent) to 0.2 percent (1/5 percent). This potency factor gives the clinician a wider range of administration than is seen with pilocarpine. The agent may be given as one drop on alternate days, twice a week, or as frequently as twice a day. More frequent use than this or in stronger concentrations does not enhance the miotic effect and may bring about side-effects.

TABLE 3

TYPES OF GLAUCOMA TREATED

Wide-angle	20
Aphakic	5
Secondary to occlusion to central retinal vein	1
Congenital glaucoma	1
Narrow-angle	0

In this study our patients were started with the stronger solutions and the frequency of administration was varied. The patients were followed daily and when we were satisfied that they were under control the time was either prolonged or the concentration of the solution was decreased. We noticed almost immediately that those patients with dark brown irises required more frequent administration and the more potent drops. Since blurring of vision was one of the complaints we instructed our patients to use the drops before retiring.

In evaluating this agent our clinical criteria of control was as follows: We considered the glaucoma to be under control if the ocular tension remained below 25 mm. Hg (Schiøtz) and if there was no further loss of visual field, and no visible evidence of progression of the disease by gonioscopy, biomiscrospy, and ophthalmoscopy.

In analyzing these cases, as shown in Table 4, we attempted to classify the patients according to control on previous medication, or uncontrolled on previous medication; compared to control on Phospholine Iodide, or uncontrolled on Phospholine Iodide. Controlled in this study means whether or not the patient was controlled with topical medication alone. Those cases that were uncontrolled by previous medication had been using in conjunction to their drops acetazolamide (Diamox). When patients using Phospholine Iodide became uncontrolled they were supplemented with Diamox. It might be added at this point that all of the patients were successfully controlled by the use of these two agents.

In Table 4 we note that 12 of the 20 cases of wide-angle glaucoma were controlled by pilocarpine and eight were uncontrolled. When these patients were started on Phos-

TABLE 4

ANALYSES OF CASES

Type	Previous Medication		Phospholine Iodide	
	Controlled	Uncontrolled	Controlled	Uncontrolled
Wide-angle	12	8	18	2
Aphakic	1	4	3	2
Secondary occlusion central retinal vein		1	1	
Congenital		1		1

pholine Iodide 18 became controlled and two remained uncontrolled. It was also noticed that the eighteen cases that were controlled had a consistently lower pressure than they had been having when on pilocarpine. In aphakic glaucoma one case was controlled by Floropryl alone and four were having to use Diamox. Phospholine Iodide controlled three of these five patients. In one case of glaucoma secondary to occlusion of the central retinal vein which was uncontrolled by pilocarpine alone, Phospholine Iodide was successful. The one case of congenital glaucoma that was uncontrolled with pilocarpine was also uncontrolled with Phospholine Iodide. In analyzing this study we note in chronic simple glaucoma Phospholine Iodide gives a much better control of the disease than pilocarpine. In aphakic glaucoma it seems to be comparable to Floropryl.

In Table 5 we have listed the side-effects that most commonly occur in the use of this longer-acting miotic agent. They are ciliary injection, brow aches and headaches, dimness of vision, nausea and vomiting, and paradoxical rise in pressure. There were nine patients out of the 27 that had no signs or symptoms. Ciliary injection was the most frequently seen sign initially but this soon subsided. Complaint of pain about the eyes, brow ache and headache were next, occurring in one third of the patients. This symptom decreased in all but two of the patients with continued use of the drug. Dimness of vision occurred in six of the patients; in three of these the medication was stopped for this reason. Paradoxical rise in pressure was not seen in this series. One patient developed a sensitivity reaction and for this reason the medication was stopped. While this patient was using Phospholine Iodide the glaucoma was under control. The sensitivity developed during the second week of use. In all, we had to discontinue the medication in four patients. In this study we had no retinal detachments, pseudomembranes, tear duct obstructions or any signs of uveitis.

TABLE 5

TOTAL CASES 27—NO SIDE-EFFECTS 9

Side-effects: Signs and Symptoms	Early	Past One Month	Medication Stopped
Ciliary injection	16	5	0
Browache and headache	9	2	0
Dimness of vision	6	3	3
Nausea and vomiting	2	0	0
Sensitivity reaction	1		1
Paradoxical rise in pressure	0		
Cells or Flare			

SUMMARY

We have reported on the effectiveness of a potent long-acting cholinesterase inhibitor, Phospholine Iodide, in the control of glaucoma. It controlled 22 of 27 glaucoma patients; percentagewise, these figures are comparable to the findings of other workers. This agent has proven to control glaucoma better than pilocarpine, not only with persistent lower pressures, but also with less frequent administrations. It has been proven comparable to DEP in the control of aphakic glaucoma.

Since glaucoma is a chronic disease the long duration of action and potency of this agent allows the clinician a wide range of

concentrations and time of administrations.

Although we encountered side-effects, we found relatively little disturbance of the patient's body physiology. However, this agent definitely causes more side reactions than pilocarpine and we feel that its use should be held in reserve for those cases that are developing a tolerance to pilocarpine. Another, but slight disadvantage, is the relative instability of the solution. When used in warm climates, Phospholine Iodide solutions should be stored in the refrigerator. The powder does not require refrigeration.

We have not used the agent long enough to notice any development of tolerance to the drug or what side effects may result from prolonged use.

Conclusion

We feel that when you consider the entire clinical evaluation of phospholine iodide, that another useful miotic agent has been added to the armamentarium for the treatment of glaucoma.

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EXPERIMENTAL STUDIES ON CATARACT FORMATION*

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Experimental cataracts have been produced in rats by feeding diets deficient in riboflavin or tryptophane (Day, et al., 1931; Curtis, et al., 1932). A lesion in rat embryos from rats fed a diet deficient in vitamin E suggested retrolental fibroplasia (Callison and Orent-Keiles, 1951).

Ferguson, *et al.* (1954) described cataracts in turkey embryos from hens fed a diet deficient in vitamin E. The effects of 2, 4-dinitrophenol on the chick embryo were re-

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ported by Feldman, *et al.* (1958) and Rigdon, *et al.* (1959). The discussion which follows is a review of some of the work done in this laboratory relating to experimentally produced cataracts, and preliminary biochemical studies relative to vitamin-E deficiency.

Observations

Embryonic mortality was observed to be high from the 24th through the 28th day of the incubation period in eggs from turkey hens fed a diet deficient in vitamin E (Ferguson, et al., 1954; Atkinson, et al., 1955). Hatchability of eggs from hens fed supplemental vitamin E was normal. The addition of vitamin E to the diet of hens increased the hatchability of eggs from 52 to 88 percent.

Embryos dying during the latter part of the incubation period were found to have cataracts in both eyes in most instances. A keratoconus condition accompanied the cataracts. A hemorrhagic, edematous area was frequently observed in the deficient embryos in the area at the base of the skull in the posterior portion of the neck.

The conditions described were from hens maintained on wire floors to prevent coprophagy, and had been fed a diet composed of natural feedstuffs, low in vitamin E, as determined by analyses of the eggs. Subsequently, another experiment was designed with a synthetic type diet, with some groups supplemented with vitamin E (Ferguson, et al., 1956). Results confirmed our earlier observations relative to vitamin E in the prevention of cataracts, and in improving the hatchability of eggs. Opacities were found in 38.8 percent of the embryos and 17 percent of these exhibited a keratoconus condition. The most conspicuous change occurred in the lens which was characterized by a liquefaction of either a part or all the lens protein. Earliest changes noted were focal areas of small Morgagnian droplets in the center or at the periphery of the lens, immediately beneath the lens capsule. There was degeneration of the lens epithelium and extensive proliferation of this area was also observed. The epithelium frequently extended to cover the posterior portion of the lens, where it is normally absent. Focal areas of degeneration were also found in the cornea.

Feldman, et al. (1958) injected eggs from chickens at various stages of the incubation period, with various levels of 2, 4-dinitrophenol (DNP). This substance has been shown to produce cataracts in hatched chicks (Robbins, 1944) and Horner (1941) reported that therapeutic use of DNP resulted in cataracts in some patients.

While temporary cataracts in chickens have been reported, permanent cataracts were found by Feldman (1958) following injection of eggs on the eighth day of incubation with 500 µg. of DNP. Other levels and ages produced only temporary damage. The cataracts produced in the chick were quite similar to that of the vitamin-E deficient turkey embryo. Furthermore, edema in the posterior neck region of the chick embryos was observed.

Rigdon, et al. (1959) also obtained a permanent cataract in chick embryos following injection with DNP. Opacities in the eyes of growing chicks and turkeys after oral administration of DNP was also reported in this study.

Preliminary biochemical studies have been made on tissues from vitamin-E deficient turkey hens. Oxygen consumption studies have been carried out on liver homogenates by conventional manometric methods with the Warburg apparatus. Results were based on nitrogen content of volume of homogenate added per vessel. The hens used in the studies had been maintained throughout their life on wire floors on a low vitamin-E diet, and had been fed a synthetic diet, deficient in vitamin E, since maturity. The hens were maintained on this synthetic diet for approximately eight

months. Prior to sacrificing, one group was continued on the E deficient diet, one group of hens was given a capsule with 29 mg. of d-α-tocopheryl acetate daily, and another group fed three such capsules daily for a period of five weeks.

Oxygen uptake was greatest in the livers of hens fed the diet deficient in vitamin E. There was very little difference in the oxygen consumption by hens fed no vitamin E or one capsule of vitamin E daily, while a statistically significant lowering of oxygen consumption was observed in the group fed three capsules daily.

Succinic dehydrogenase activity was found to be very high in the heart and liver of vitamin-E deficient hens, and greatly decreased in the birds provided supplemental vitamin E. Biochemical studies similar to those described above are now in progress.

Summary

Experimental cataracts have been produced in turkey embryos by feeding hens diets deficient in vitamin E. Cataracts in the deficient embryos show extensive liquefaction of lens protein, proliferation of the lens epithelium and focal areas of degeneration in the cornea. Cataracts have been produced in chick embryos following the injection of DNP into the egg.

Preliminary biochemical studies indicate that oxygen uptake by the liver and succinic dehydrogenase activity of the liver and heart are increased in vitamin E deficiency.

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DINITROPHENOL-INDUCED CATARACTS IN THE AVIAN EMBRYO*

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The ability of dinitrophenol to induce cataracts has been known since the 1930's.[1] Of all experimental animals the chick appears to be the only one which is consistently susceptible to the drug. The lesion which is produced is reversible and grossly resembles the transitory opacities induced by heat, cold, anoxia, osmotic changes and others. Loomis and Lipmann[2] showed that dinitrophenol stimulated oxygen consumption but decreased the incorporation of inorganic phosphate into high energy phosphate compounds. This phenomenon is referred to as an uncoupling of oxidative phosphorylation. It is this property of the drug that led us to its use in our studies.

In some of our earlier work Ferguson[3, 4] showed that a deficiency of vitamin E resulted in the formation of cataracts in turkey embryos. These lesions were not observed in mature birds unless the birds were raised from a cataractous poult. Vitamin-E deficient tissues consume oxygen at an elevated rate with a concomitant uncoupling of oxidative phosphorylation.[5] The susceptibility of the vitamin-E-deficient embryo to cataract formation plus the basic similarity between this deficiency and dinitrophenol toxicity in uncoupling oxidative phosphorylation suggested that the drug might produce a permanent lesion if injected into the incubating egg. A study was initiated to investigate this possibility, for if true it would provide a valuable tool for studying the mechanism of cataract formation. This paper deals with the results of that study.

EXPERIMENTAL PROCEDURE

Solutions containing 1.0 to 1,000 μg. of dinitrophenol were injected into chicken eggs through a hole drilled into the air cell. The injections were made either prior to incubation or after one to 15 days of incubation. Regardless of the time of injection the range of doses was selected to provide minimum and maximum toxicity.

The dinitrophenol solutions were prepared by diluting a stock solution with physiologic saline. The stock solution was prepared by dissolving 200 mg. of dinitrophenol in dilute sodium hydroxide to provide a concentration of sodium ion equivalent to physiologic saline and then adjusting to pH 7.4 with dilute hydrochloric acid.

The eggs were incubated under normal conditions for the 21 days required to hatch a chicken egg. At the end of this time all the chicks and live unhatched embryos were killed by decapitation. The lens and vitreous humor of one eye was excised through an incision in the sclera of the posterior of the eye. The lens was examined under a dissecting microscope with indirect illumination. The opposite eye was removed intact and preserved in 10-percent formalin for histological sectioning.

RESULTS

GROSS OBSERVATIONS

Cataracts were observed grossly in embryos and chicks hatched from eggs which had been injected with dinitrophenol after

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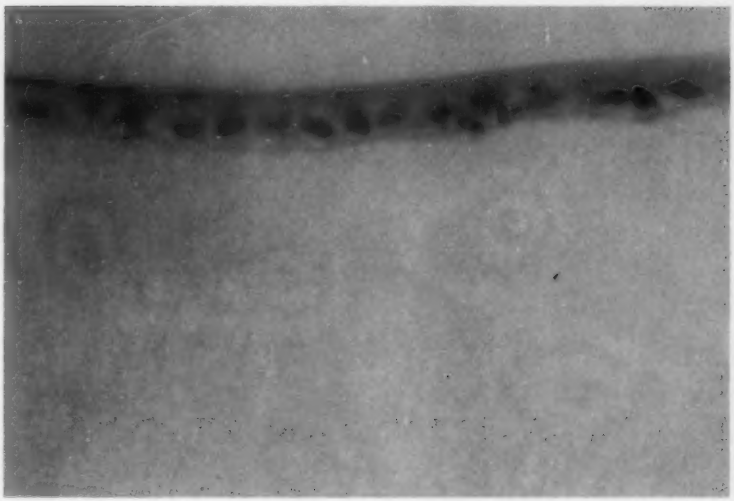

Fig. 1 (Feldman, Ferguson and Couch). Anterior marginal epithelium of the lens of a day-old chick. Note the single-cell thickness.

eight days of incubation. Injecting the drug before the eighth day failed to induce a lens lesion except in one isolated instance of a precocious embryo. The incidence of cataract induction declined in groups injected after the 11th day. A dose of 1.0 mg. of dinitrophenol produced twice as many cataractous chicks when injected on the 11th day as it did when injected on the 13th day, yet the mortality was not affected. The cataract appeared grossly as a small white spot in the center of the lens when viewed from its anterior face. The spot was occasionally accompanied by a peripheral opacity, the incidence of which was greatest in the unhatched embryos. In addition to the cataracts, the back of the neck of the unhatched embryos was usually greatly enlarged, yellow and gelatinous in nature, and frequently so transparent that the vertebrae could be easily seen. Hemorrhaging was frequent in this area. These gross observations are similar to those observed in the vitamin-E deficient turkey embryo.

Microscopic findings

1. *Anterior marginal epithelium.* No degenerative changes were observed in the lens epithelium from the cataractous birds. This tissue is normally one cell in thickness across the anterior face of the lens but thickens at the lens equator to form the annular pad, a characteristic of birds and reptiles (figs. 1 and 2). The epithelium was frequently thickened by proliferation in the cataractous birds (fig. 3). In many sections we observed convolutions in the band of nuclei through the annular pad (fig. 4). At first, we thought that this was related to the appearance of peripheral opacities but later these convolutions were seen in control embryos as well. However, occasional areas of degeneration were seen in the convoluted portion which did correlate with the appearance of peripheral opacities.

2. *Lens cortex.* Degeneration in the cortex was observed in our experiments as early as 48 hours after injection of the drug. Small focal areas of degeneration were seen at the posterior of the cortex, in the cortical area directly beneath the epithelium and in the lens nucleus. Rigdon,[6] in a collaborative study with us, reported the appearance of histologic evidence of degenerative changes in embryos eight hours after injection. The earliest change he observed was edema.

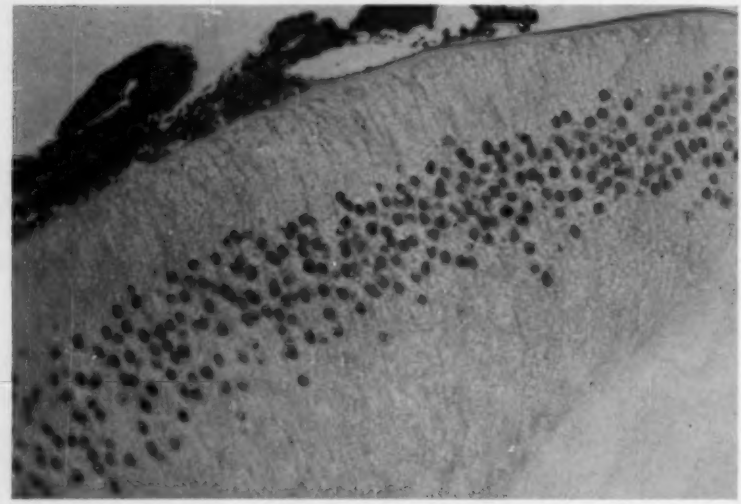

Fig. 2 (Feldman, Ferguson and Couch). Annular pad at the lens equator. This structure is found in birds and reptiles and arises by a thickening of the epithelium. Note the regularity of the nuclei of these cells.

There was some swelling of the lens fibers and varying degrees of nuclear degeneration. In many sections there were small focal areas of degeneration scattered throughout the cortex. The smooth curving band of lens fiber nuclei was greatly disrupted in the cataractous lens causing these nuclei to exhibit a very disorderly arrangement (fig. 5). In some cases these nuclei appear to have moved toward the posterior face of the lens where nuclei are normally absent (fig. 6). A few sections exhibited

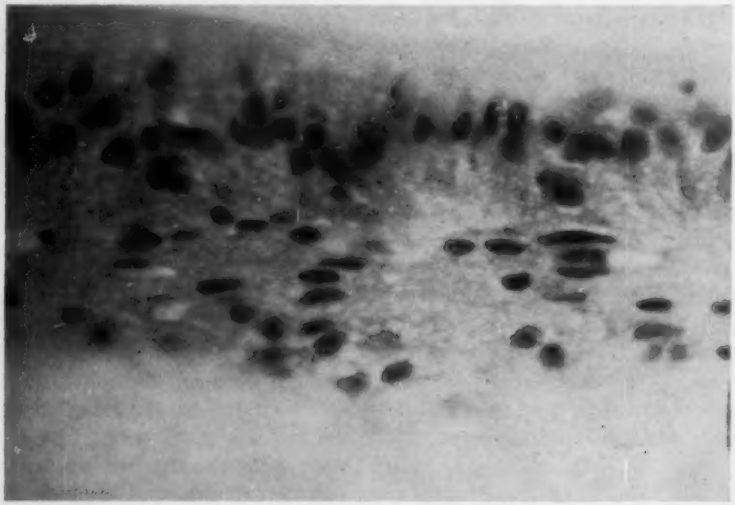

Fig. 3 (Feldman, Ferguson and Couch). Anterior marginal epithelium of the cataractous lens of day-old chick showing thickening by proliferation.

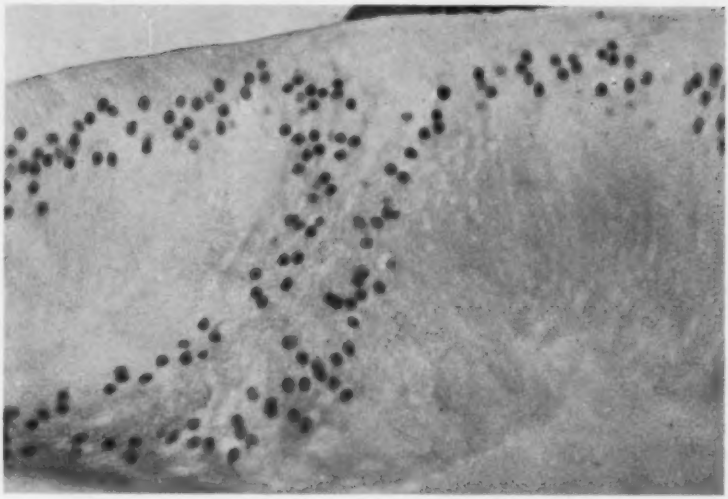

Fig. 4 (Feldman, Ferguson and Couch). Convolutions of the band of nuclei through the annular pad of a cataractous lens. In this case a peripheral opacity was also observed.

very widespread degeneration. The area directly under the epithelium had degenerated laterally and posteriorly producing a T-shaped lesion (figs. 7 and 8). The entire cortex adjacent to this massive area of necrosis showed evidence of liquefaction and degeneration. A similar lesion is seen in the vitamin-E deficient turkey embryo.

Comment

The development of the eye has been studied very intensively with regard to its

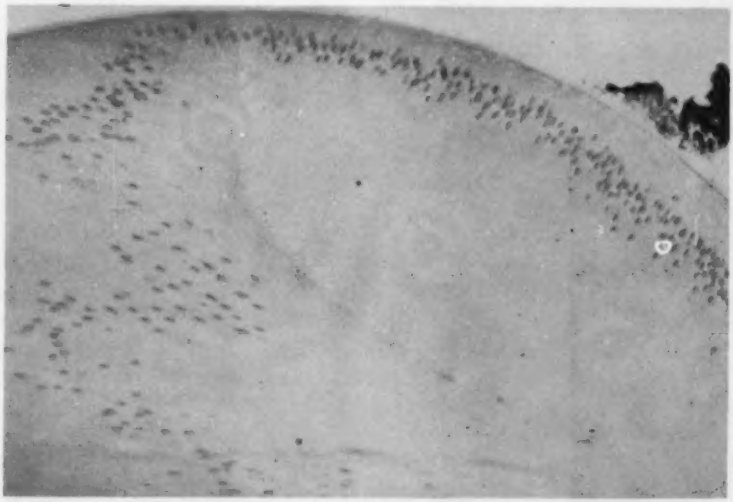

Fig. 5 (Feldman, Ferguson and Couch). Annular pad and section of the cortex of a cataractous lens. Note the irregular arrangement of the lens fiber nuclei. Normally these occupy the center of the lens fibers and form a smooth, regular band through the cortex. In the center of the figure a large area of liquefaction with small focal areas of degeneration can be seen.

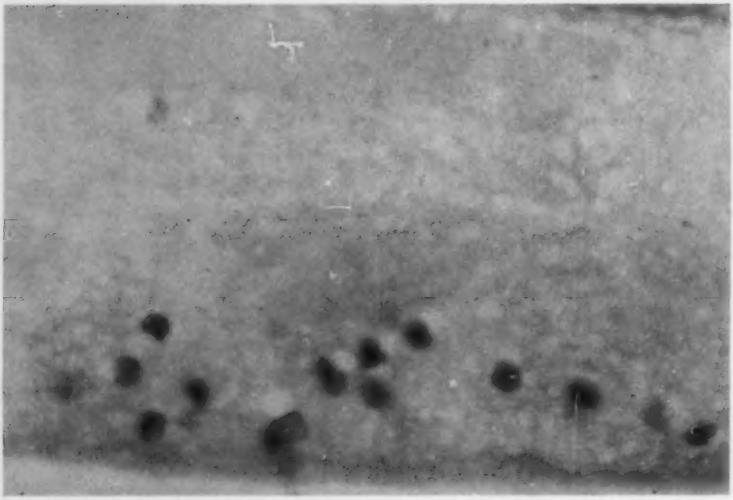

Fig. 6 (Feldman, Ferguson and Couch). Posterior face of a cataractous lens. Note the nuclei which are normally absent from the posterior face of the lens.

morphology and physiology, but very little is known of its biochemistry. Several enzyme systems have recently been defined in the developing rat lens and cornea.[7] Those of the lens are of particular interest. It is suggested that as the development of the lens proceeds, the activity of the Krebs cycle enzymes declines in the cortex and nucleus but increases in the epithelium. These findings also suggest that glycolytic enzymes are static in the epithelium but increase very markedly in the cortex and nucleus. Unfortunately these data only concern themselves with a few enzyme systems. Although in-

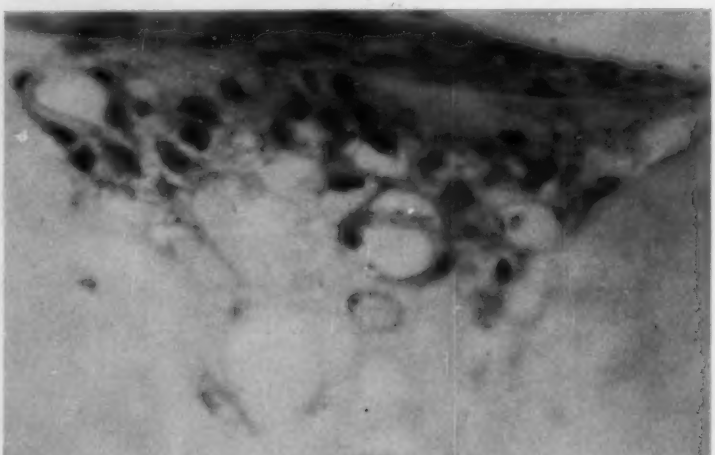

Fig. 7 (Feldman, Ferguson and Couch). Area of degeneration at the posterior face of the lens. Note the nucleated cells at the top of the figure.

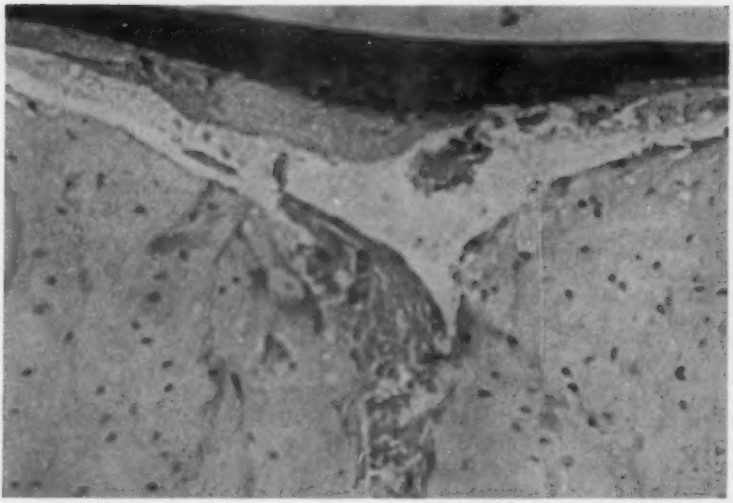

Fig. 8 (Feldman, Ferguson and Couch). T-shaped lesion in a cataractous lens. Note extensive proliferation of the anterior marginal epithelium and the extensive degeneration beneath it.

complete, they are interesting when the findings of Kinsey and Frohman[8,9] are considered. These authors reported that the oxidative enzymes of the adult lens are found only in the epithelium while the cortex is primarily glycolytic. Consequently, the cortex is dependent on the epithelium for a supply of adenosine triphosphate (ATP) with which to carry on its metabolism.

These findings are of great importance in studying the mechanism of cataract formation. Failure to produce dinitrophenol-induced cataracts in the chick embryo prior to the eighth day of incubation indicated that a major change in the metabolism of the lens occurs at this time which renders the lens susceptible to cataractogenesis. The embryonic lens fibers arise by an elongation of the proximal wall of the lens sac towards the distal wall.[10] Initially this lens primordia is epithelial in nature and probably has the metabolic activity of epithelial cells. Whether this metabolic activity changes after differentiation and morphogenesis is not known.

Dinitrophenol prevents the formation of ATP by the process of oxidative phosphorylation. Since the cataract was produced only after seven to eight days of incubation, it is possible that the elongated lens sac cells continue to carry out the metabolic activity of epithelial cells until that time and hence would not require an outside source of ATP. It is significant that dinitrophenol has no effect on substrate-level phosphorylations and a supply of ATP could be derived from this source for the metabolism of the lens. Consequently, a cataract would not result until such time as the cortex becomes dependent on the epithelium for its supply of ATP. Furthermore, in the dinitrophenol-induced cataracts the opacity is found only in the cortex, never in the epithelium, again pointing out the effect of the dependence of the cortex on the epithelium for its supply of ATP. The synthesis of ATP by substrate level phosphorylation in the epithelium is probably not adequate to meet the requirements of both tissues.

The relative ease with which cataracts can be produced in the chick embryo makes them an ideal organism with which to study cataract formation. Furthermore, the basic histologic similarity between dinitrophenol-induced cataracts in the chick embryo and those produced in other species by other

means suggests that the same basic biochemical pathways of metabolism may be involved.

The elucidation of these pathways may provide a means whereby human cataracts can be prevented or cured.

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MYCOTIC FLORA OF THE CONJUNCTIVA*

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Introduction

In recent years, numerous cases of intraocular fungal infections have been reported. Since many of the infections have occurred after surgery, trauma, and topical cortisone therapy, it appears that they are exogenous in origin. If this is true, the normal fungal flora of the eyes becomes extremely important, because these organisms may be the source of the intraocular infection.

Surprisingly few studies have been made of the normal fungal flora of the human eye. Only two detailed reports concerning such flora have appeared. One was conducted by Fazakas, a Hungarian worker, in 1934, and the other by Matsui and Hanabusa, two Japanese workers, in 1955. Fazakas cultured 160 normal eyes and obtained 39 positive cultures (24.3 percent) for fungi. Matsui and Hanabusa determined the effect of prolonged local corticosteroid therapy upon the incidence of fungi in the eye. The control group of 65 patients yielded fungi in 12 cases (18.5 percent). In contrast, 42 of the 62 patients on local corticosteroid therapy had positive cultures. (67 percent).

It seemed then worthwhile for us to study the incidence of the mycotic flora of the eye. By such a study we hoped to establish: (a) whether the incidence of the fungal flora of the eye was approximately the same in this country as in other parts of the world; (b) whether the incidence of these organisms varied between different age groups, and (c) whether the organisms we found inhabiting the conjunctiva were capable of producing an intraocular infection. This last objective we hoped initially to study by comparing the organisms we isolated with those fungal organisms previously reported to have caused an endophthalmitis. As a corol-

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lary project, we were interested in studying the sensitivity of the isolated organisms to the newer antifungal drugs (Nystatin and Amphotericin B).

Procedure

The conjunctival sac of each eye of 156 adults, 52 infants and 52 children were tested for the presence of fungi. Patients were chosen at random from the clinics, hospital wards, and nursery. They were first examined to rule out any external disease of the eyes before cultures were taken. No patients receiving corticosteroid therapy, either locally or systemically, were included in this study.

The procedure used in testing eyes was as follows. The lower lid was pulled down and the conjunctival sac swabbed with a sterile cotton applicator moistened with saline. This swab was first stroked across a mycosel slant and then subsequently across a Sabouraud's slant. Slants were used instead of Petri plates in order to reduce the possibility of air contamination. Sabouraud's agar is essentially a starvation media containing peptone, dextrose and agar, and allows the growth of both pathogenic and non-pathogenic fungi, while inhibiting the growth of bacteria. Mycosel is a more complex media containing chloramphenicol and cyclohexamide. The chloramphenicol inhibits a broad spectrum of bacteria and cyclohexamide inhibits all the common air-borne fungi (usually called "contaminants"). Thus mycotic "pathogens" grow on mycosel, whereas "nonpathogens" normally do not grow on this media. However, as will be pointed out later, many of the so-called nonpathogens for man probably are capable of producing an endophthalmitis if introduced into the eye.

In order to give greater significance to the findings, the frequency with which usual air-borne fungi would fall into the culture tubes or on the swabs was determined in the following manner. A sterile swab was removed from its tube, taken through the same movements as was necessary to swab an individual's eyes, and exposed to the air for the usual length of time required to carry out the test. It was then stroked on Sabouraud's slant. Fifty slants were inoculated in this fashion.

All positive cultures were allowed to grow out to sufficient size, after which they were isolated and identified as to genus. The molds were identified by their colonial morphology and the appearance of typical microscopic structures as found in a sample of the colony examined on a glass side in a few drops of cotton blue under a glass cover slip.

Pigmented yeasts were studied for ballistospore formation. Tests determining the drop excretion of spores were performed for this purpose. None of the pigmented yeasts in this study produced ballistospores.

The white yeasts were studied by testing their growth at 37°C on Sabouraud's media. The white yeasts that did not grow at this temperature were considered nonpathogenic for man and no further identification was attempted. The yeasts growing at 37°C were readily identified as Candida albicans by chlamydospore formation on corn meal agar.

Studies were then carried out to determine the sensitivity of the fungi to Amphotericin B (Squibb) and Nystatin (Squibb). Because Amphotericin B diffuses into agar very poorly, the use of impregnated discs was not possible with this agent. Accordingly, Petri plates were prepared, using media containing serial dilutions of Amphotericin B. The various plates contained the following concentrations of Amphotericin B: standard (none); 1.56 μg./ml.; 6.25 μg./ml.; 25 μg./ml.; and 100 μg./ml. After the agar had set, the plates were inoculated with the test organisms. To determine sensitivity to Nystatin, standard sensitivity discs impregnated with nystatin were placed on the surface of agar plates previously inoculated with the fungi. Observations were made at regular intervals to evaluate the inhibition of the fungi by Amphotericin B and Nystatin.

Results

The first group consisted of 156 adults (age range 22-85 years) made up mainly of patients from the surgical and medical clinics of the Medical Center. Cultures from these 312 eyes were positive in 32 (10.3 percent). The 32 positive cultures were obtained from the eyes of 25 patients (16 percent). Five of these patients had a positive culture in each eye and one individual had two organisms in one eye and a third fungus in the opposite eye. From the 32 positive cultures, 20 molds and 12 yeasts were isolated. Seven of these yeasts were pigmented and five were nonpigmented or white yeasts.

The second group studied consisted of 52 children from the Pediatric clinic. These children ranged in age from two months to 16 years. Cultures from these 104 eyes gave a total of five (4.8 percent) positive tests, each from five different patients. All the isolated organisms proved to be molds.

The third group studied consisted of 52 newborn infants from the Medical Center nursey. These infants ranged in age from one-half hour to three days. Cultures of these 104 eyes gave only one (0.1 percent) positive test; this was a pigmented yeast.

None of the 50 control slants for possible air contamination were positive.

The results of the survey and the identification of the organisms are summarized in Tables 1 and 2.

Sensitivity studies

All of the organisms were inhibited by Amphotericin B, with most of them being inhibited even by the lowest concentration of Amphotericin B used (1.56 μg./ml.). In a few cases there was a small amount of growth that could be seen in the agar plates that contained Amphotericin B. However, this growth showed a vertical bushy pattern rather than the horizontal soft type of growth normally exhibited by fungi.

After the tests with the Nystatin discs had been performed, it was found that these discs had been used beyond the recommended expiration date. Therefore, all of these observations have been discarded.

TABLE 2

Fungi Isolated

Organism	Number Isolated
Mycelia sterila	14
Penicillium	3
Dematiaceous	3
Cladosporium	3
Aspergillus	2
Alternaria	3
Clasterosporium	1
Eurotium (ascomycetes)	1
Rhodotorula	7
Candida albicans	2
White yeasts (no growth at 37°C.)	2
White yeasts (growth at 37°C.)	1

Comments

With such a high incidence of mycotic flora in the normal healthy conjunctiva, it would seem quite likely that intraocular infections with these fungi may result from the introduction locally of the organisms rather than by contaminated instruments used in surgery and trauma. This possibility has recently been emphasized by Fine and

TABLE 1

Results of cultures

	Number of Eyes Cultured	Positive Cultures			
		Sabouraud's Media	Mycosel Media	Total No. of Fungi	% of Cultures Positive
Adult	312	31	1	32	10.3
Children	104	4	1	5	4.8
Newborn	104	1	0	1	0.9
Control	50	0	0	0	0

TABLE 3

MYCOTIC ORGANISMS IN ENDOPHTHALMITIS FOLLOWING SURGERY AND TRAUMA (REPORTED CASES)

1.	Aspergillus*
2.	Blastomycetes
3.	Actinomycosis
4.	Candida*
5.	Cladosporium*
6.	Valuntella
7.	Cephalosporium
8.	Curvularis
9.	Penicillium*
10.	Gibberella

* Similar organisms isolated in this study.

Zimmerman. Although these floral fungi do not cause any reaction in the normal conjunctiva, they may very well be pathogenic when introduced into the eye as suggested by Anderson and his co-workers. Substantial evidence for this is offered by comparative studies of the organisms that were found in this series and organisms that have been reported by other investigators to have caused an intraocular infection (table 3). In this respect the inner eye may react to these fungi much as it does to certain bacteria, such as the severe reaction to Bacillus subtilis, usually considered nonpathogenic in any other part of the body.

It is interesting that the incidence of mycotic organisms in the healthy eye in this series is very similar to the incidence found by two other workers in different parts of the world. Theoretically, one would feel that certain environmental factors would alter the incidence of organisms obtained—the time of the year, humidity, rainfall and wind. Various studies by mycologists indicate that the concentration in air of the spores of fungi are in greatest number during the summer and early fall season. In the southern United States, there is less seasonal variation than in the north. On windy days the counts of atmospheric fungi are higher. While dampness generally favors the growth of fungi, air-borne fungi are numerous in dry climates, indoors as well as outdoors. This survey was performed in July and August; the weather was quite hot but only moderately humid. There was not unusual dampness or heavy wind.

A record was kept of occupations of the patients but there was no positive correlation with occupation and incidence of fungal organisms. However, most of our patients were people who worked out-of-doors—farmers, laborers, and so forth.

The children came mainly from an urban rather than a rural area as did the adults. Although no sampling for fungi was done in the different areas, it is likely that the incidence of air-borne fungi is higher in the rural rather than the urban areas. This might explain the large difference in incidence between adults and children.

The low incidence of fungi in the newborn would seem to confirm the fact that these fungi are air-borne into the conjunctiva. The nursery in which the newborns were tested is quite free from air contamination. All the air entering the nursery is filtered. Moreover, the newborns eyes are closed most of the time; consequently, the possibility of air contamination would be minimal.

It should be pointed out that the organisms isolated are exactly those usually isolated from plates exposed to air. Although these organisms are found in the normal conjunctiva, the pathogenesis of an intraocular infection resulting from such fungi remains obscure.

SUMMARY

The occurrence of fungi in the normal conjunctival sac was determined in 520 eyes of healthy adults, children and newborns. Cultures were positive in 10.3 percent of the adult eyes, five percent of the children's eyes, and 0.1 percent of the newborns' eyes. Controls were run to exclude air contamination of the culture tubes.

The organisms obtained were similar to fungi previously reported by other workers to have caused intraocular infections following surgery or trauma. It is suggested that intraocular mycotic infections may result

from local introduction of the fungal flora of the conjunctiva. Though the organisms are nonpathogenic in the conjunctiva, they may be capable of becoming pathogens inside the eye. All of the cultured organisms were inhibited by Amphotericin B.

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RESPONSES AND DISTRIBUTION OF THE HUMAN INTRAOCULAR MUSCLES*

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The pupil constricts and dilates, suggesting circumferential and radial contractile forces in the iris. Up till now, experiments attempting to locate the sources of this contractility have been performed on the irises of laboratory animals.[1, 3, 5–7, 10, 11, 14, 18–20, 22–26, 29–33, 39, 41–43, 50] In these experiments, isolated rings contracted circumferentially to cholinergic and relaxed to adrenergic drugs; isolated sectors contracted radially to both cholinergic and adrenergic drugs as well as to electric current. The findings on radial contractility were inconsistent with the hypothesis that the so-called "dilator pupillae" contracts upon sympathetic stimulation, thereby widening the pupil.

Recent reports from this laboratory indicate that in the cat the ciliary muscles, rather, are the source of the radial contractility.[2] Examination of the irises of the cat and other laboratory animals reveals that the distribution of histologically identifiable muscle fibers seldom resembles the human, a fact well-known to veterinarians.[45] What is more, there is still some doubt whether the "dilator pupillae" of any species actually is composed of muscle cells.[8, 9, 15–17, 21, 27, 33, 34, 37, 40, 44–46] Therefore, identification of the distribution and responses of muscle in the hu

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man iris requires the application of the crucial test for muscle; that is the development of active tension in response to appropriate stimulation.

The purpose of the present study was to apply these tests to the three alleged muscles inside the human eye.

Method

Eyes enucleated either for indicated surgery or shortly postmortem were used. The iris was selected for study only if the sphincter, a known muscle, was in good condition, evidenced by prompt constriction of the pupil after the cornea and adjunct sclera were removed (fig. 1). When the pupil reached maximal constriction, slits 1.5 mm. long were cut through the entire thickness of the exposed uvea in the radial and circumferential directions in three areas, pupillary, ciliary, and intermediate between them. Two millimeters of tissue surrounding each slit was excised.

Isometric tensions developed by these isolated segments following exposure to graded doses of epinephrine (adrenalin), methacholine (Mecholyl), electric current and cooling were measured in an apparatus already described.[2] By testing segments from pupillary, intermediate and ciliary regions, the sphincter, "dilator" and ciliary muscles could be tested separately. What is more,

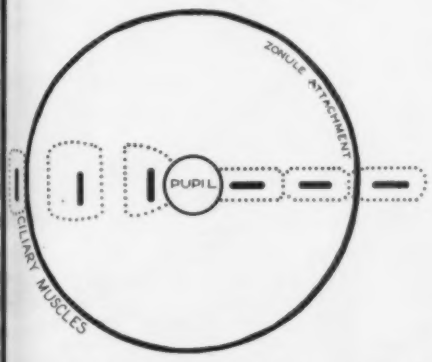

Fig. 1 (Apter). Diagram of the human iris. Solid lines indicate slits. The dotted line is the outline of the excised segments.

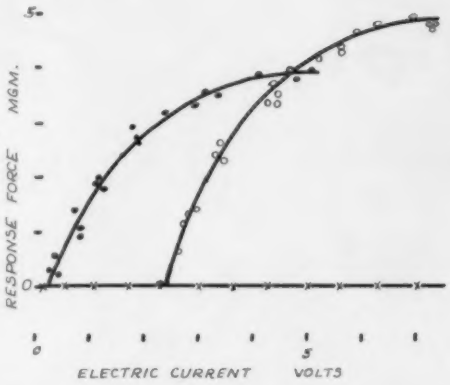

Fig. 2 (Apter). Strength-stimulus curve for segments in which the central slit was cut in the radial direction. Points are actual data corrected to adjust scales. The curves are fitted forms of equation 1.

Open circles are values from six specimens of ciliary muscles, closed circles from seven specimens of sphincter, crosses from 10 specimens of "dilator."

the strength of the muscles could be quantitively compared since all were tested at the same resting tension.[12, 13] Moreover, the response to temperature clarified the properties of segments whether muscle or not.[3, 4, 38, 47–49]

Results

Figure 2 shows dose-response curves for electric current in the radial direction. These were chosen for illustration because electric current is a nonspecific stimulus that never fails to induce contraction in a tissue containing muscle. It demonstrates that the sphincter and ciliary muscles, containing typical muscle fibers, gave an intensity-response curve, like cats and dogs, monotonic in form, with the concavity downward, reaching an asymptote at maximal response.[5] This curve fit an exponential form as follows:

$$F = F_{max}\left[1 - e^{-\frac{D - D_t}{1.4(D_{50} - D_t)}}\right] \qquad (1)$$

where F is the tension developed to strength D, D_t is threshold strength, F_{max} is maximal response, and D_{50} is the strength of stimulus inducing 50 percent of F_{max}. This systematic behavior gives strong support to the as-

TABLE 1

RADIAL CONTRACTILE FORCES

	Sphincter		"Dilator"		Ciliary Muscles	
	No.	Force (max.)	No.	Force (max.)	No.	Force (max.)
Mecholyl	4	3.1	6	0.5	5	3.2
Adrenalin	3	− 2.7	8	−0.5	4	2.9
Current	7	3.9	10	0	6	4.7
CIRCUMFERENTIAL FORCES						
Mecholyl	4	16.1	10	0	3	3.1
Adrenalin	3	− 5.9	14	0	3	3.9
Current	7	15.8	7	0	6	3.0

sumption that the methods used in this study dependably demonstrated contractility where it existed. Yet these same methods failed to demonstrate contractility in the dilator, as Figure 2 shows.

Table 1 is a resume of mean maximal forces obtained from the three separate muscles in radial and circumferential directions. A negative sign indicates that the stimulus induced a drop in tension. The sphincter contracted to Mecholyl and to electric current but relaxed to adrenalin, greater changes in tension occurring in the circumferential direction. The ciliary muscles contracted to all three stimuli with the same power in both directions. The table does not show it, but tensions were doubled if both drugs were used simultaneously. The dilator did not respond at all.

Figure 3 illustrates the changes in resting tension induced by temperature alterations in the environment of the sphincter, ciliary and "dilator" muscles. It is apparent that the sphincter and ciliary muscles have a negative sigmoid relationship, higher tensions occurring at lower temperatures. This is characteristics of smooth muscle.[3, 4, 25, 38] The terms f_{max} and f_{min} refer to the highest and lowest tensions reached in the range of temperatures considered. The force (f) at any absolute temperature (T) then may be expressed as

$$f = \frac{f_{max}e^{C/T} + f_{min}}{1 + e^{C/T}} \qquad (2)$$

where C is the proportionality factor. The "dilator," on the other hand showed only a slight change in tension with temperature changes, these taking the form

$$f = kT + I \qquad (3)$$

where k is a new proportionality factor and I is the force to be read at absolute zero temperature. Again, "dilator" did not act like muscle.

DISCUSSION

The important new findings are that the human "dilator pupillae" fails to act like muscle; that the ciliary muscles contract to both adrenalin and Mecholyl; that the sphincter can contract slightly in the radial direction. This discussion will handle the following three questions: (1) Why is it that the "dilator" pupillae was ever labeled muscle? (2) If the dilator is not muscle what is it? (3) What clinical applications

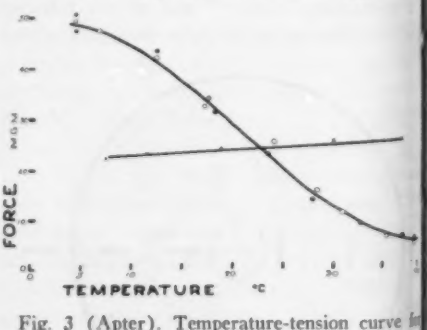

Fig. 3 (Apter). Temperature-tension curve for each of the three intraocular muscles. The points are actual data corrected to adjust scales. The sigmoid curve is a fitted form of equation 2. The straight line is a fitted form of equation 3.

Open circles are mean values froms seven specimens of ciliary muscles; closed circles, 13 specimens of sphincter muscle; crosses from 19 specimens of "dilator."

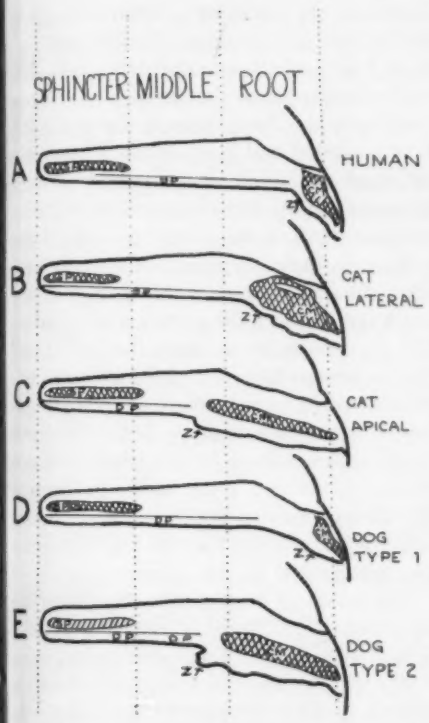

Fig. 4 (Apter). Diagrammatic cross-section of the irises of three species. See text.

may be made of the new information?

To treat question one, Figure 4 is inserted, showing a schematic cross-section of irises of humans, cats and dogs. The information on the cat and dog were obtained in this laboratory but are well-known to veterinarians.[45] It is apparent that the distribution of sphincter and ciliary muscles differs among species, explaining why experimenters thought that demonstrated contractility lay in the "dilator." All of the trouble seems to stem from the fact that their experiments were done on cats, but the histology they relied on was done on humans.

This incorrect assumption gave rise to the following misconception. If an electrode is placed on the sclera of a cat and of some dogs, the pupil margin will move toward the electrode when the current is turned on. This is a classical experiment performed by Langley and Anderson in 1892[29] and has been repeated many times since. Recently, a circumferential[31] slit in the middle portion of the cat iris left in situ, showed that this radial contractility was in the ciliary part of the iris, not in the sphincter. Figure 4 shows, however, that the ciliary region of the cat iris is a solid mass of smooth muscle fibers continuous with the ciliary muscles, making it erroneous to conclude that such radial contractility resides in the "dilator." Since the ciliary muscles extend into the iris in some dogs and not in others, it is logical to suppose that the dog iris acted like the cat iris when the dog ciliary muscles were arranged like the cat. But in instances when the dilator pupillae was tested alone[2] it did not respond to any stimulation. Even more, the dilator of the human, besides not resembling muscle in appearance, failed in all respects to behave like muscle.

It remains, therefore, to discover what the dilator is. Some progress is made by describing the behavior, to temperature, of iris segments containing this membrane. The behavior is characteristic of elastic polymers.[47–49] This is not surprising since the "dilator" resembles a cuticular membrane in many features: it is acellular, it is intimately connected with, even inseparable from, a layer of epithelial cells; it is continuous with a cuticular membrane of the ciliary body and the choroid. If it is cuticular, it could have elastic properties resembling those other cuticular membranes: the lens capsule and Descemet's membrane. It would gape after incision; be restored after stretch, elucidating some clinical observations. Most important, it should respond to physical changes like elastic polymers. The present study supplies information about one such agent, temperature. The "dilator pupillae" does respond characteristically to it.

The present findings also suggest possibilities for interpreting normal reflex responses of the intact pupil. For example, the

photic responses of the pupil are abolished by interference with the parasympathetic nerve supply and are unaltered by similar interruption of the sympathetic supply. The current interpretation that the "dilator pupillae" induces dilation is not consistent with these clinical and experimental facts and must be abandoned for lack of physiological evidence that it is a muscle. There is no reason to assume anything more than sphincter action and elastic recovery to explain the photic responses of the pupil. It cannot be stated at this time that the radial ciliary muscles play no role at all, but they do not seem necessary.

However, when we examine pupillary responses to accommodation, there is a distinct possibility that the ciliary muscles may be involved. Heretofore, it has been assumed that the sphincter mediated this response via special nerve pathways for lack of other mechanisms. With the present results, it is possible that the ciliary muscles are concerned, certainly in cats and dogs, but also in humans. In favor of this idea, even though the ciliary muscles are peripheral in humans, is that after removal of the iris sphincter, the remaining iris root constricts to accommodation but not to light. Also, the Argyll-Robertson pupil, insensitive to light by virtue of a damaged iris, still responds to accommodation. It appears possible from these examples that the ciliary muscles may, indeed, alter the size of the human pupil, especially in accommodative responses.

It seems in order to clarify, also, pupillary dilation to orthosympathetic mediators, either liberated by iridal nerves or by adrenal gland or instilled as drugs. The excess dilation they induce may be explained by the relaxation of the sphincter combined with contraction of the ciliary muscles. Naturally, such an action should be most effective in the absence of parasympathetic control. Indeed it is, in the presence of atropine.

Besides demonstrating the probable properties of the dilator, these studies on the intraocular muscles give some new information about the action of autonomic drugs on the intraocular muscles. Parasympathomimetic and sympathomimetic drugs both contract ciliary muscles; while the former contracts and the latter relaxes the sphincter. It is conceded that part of the ameliorative action of cholinergic drugs on narrow angle glaucoma is to pull open the canal of Schlem by contraction of the ciliary muscles. If that is the case, then a combination of cholinergic and adrenergic drugs could allow a dilated pupil and yet keep the angle opened. Indeed, this appears to be the case. Becker[28] found that a parasympathomimetic drug given to a patient with a narrow angle, inducing pupillary constriction may safely be followed with neosynephrine, even if the pupil widened. Probably, the two types of drugs contract the ciliary muscles synergistically, thereby opening the angle, while the two are mutually antagonistic on the sphincter.

The action of temperature changes on the intraocular muscles also suggests possible clinical applications. Cold contracts all intraocular muscles and this is what one hopes to achieve in acute glaucoma. Moreover, cold also constricts muscle-bearing arteriolar walls (but not the amuscular veins). It seems possible that the following combined effects brought on by lowering the intraocular temperature might be synergistic in ameliorating a closed angle: (1) contract all intraocular muscles, thereby opening the angle; (2) constrict arterioles, reducing the formation of aqueous humor; (3) leave veins open, allowing unhampered outflow of aqueous. However, tests would have to be carried out on suitable cases with tonography before clinical use could be made of this agent.

Clinical application may also be made of the knowledge that warming the muscles relaxes them. This is what we aim for in cataract extraction. When a pupil remains tight despite medication, raising the temperature slightly and carefully aids in relaxation of the muscles of cats and dogs. It may prove useful clinically.

Summary

1. Using a technique which successfully isolated each of the three alleged human intraocular muscles, the distribution and responses of these muscles to graded stimulation were quantified.

2. The sphincter muscles contracted both radially and circumferentially to Mecholyl and electric current, but relaxed to adrenalin.

3. The ciliary muscles contracted equally in both directions to adrenalin, to Mecholyl and to electric current. The effects of adrenalin and Mecholyl were summated.

4. The dilator pupillae did not respond at all.

5. The responses of sphincter and ciliary muscles to stimuli were systematic, fitting an exponential curve that is defined in the text.

6. The sphincter and ciliary muscles showed a negative sigmoid correspondence between temperature and resting tension. The dilator showed a slight positive linear correspondence.

7. The responses of the sphincter and ciliary muscles were typical of muscle.

8. The response of the dilator was characteristic of an elastic polymer.

9. A re-evaluation of previous experiments and of clinical observations was possible.

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THE MACROPHAGES OF THE HUMAN VITREOUS BODY*

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The cellular elements of the vitreous body of the human eye have recently become of great interest to a number of researchers in Ophthalmology. As a part of studies of this field the present demonstration deals with the nature, origin, and function of the macrophages of the human vitreous body. It must be emphasized that these macrophages are not a normal constituent of the vitreous body. However, these simple cells are very commonly found in the vitreous under many different pathological conditions.

The reaction of the macrophages invading the vitreous is only part of a group of several reactions that may be found in the vitreous of diseased eyes. Some of these are the invasion of inflammatory cells, vitreous exudation and hemorrhage, and retinitis proliferans. In most cases of pathologically involved vitreous there is a combination of the reaction of the macrophages with those of inflammatory cells or fibroblasts or with bleeding. The reaction of the macrophages is very commonly seen secondary to vitreous bleeding or exudate.

The case used for this demonstration exhibited a reaction of virtually only the macrophages secondary to an extensive vitreous exudate. All the known phases of the migration and evolution of these cells during their phagocytic activity can be seen in the slides of this single eye. This fact makes it an ideal case for this demonstration.

This case is one of a rare slow-growing tumor in the peripheral retina of a child. A part of this eye was sent to me by Dr. Lorenz E. Zimmerman of the Armed Forces Institute of Pathology, Washington, D.C. The case had already been studied and diagnosed by Dr. Zimmerman and also by Dr. S. Ry Andersen of Copenhagen. Both agreed that the tumor represented a rare retinal neoplasm that was classified as an intermediate between a typical medullo-epithelioma and a retinoblastoma. This tumor protruded into the posterior chamber of the eye and had resulted in a pre- and retroretinal dense gelatinous exudate and a virutally pure macrophagic reaction all through the vitreous.

Method of examination

Most of the eye was fixed and imbedded in paraffin at the A.F.I.P. A part of the eye with an area of the tumor, the retina, vitreous, choroid, and sclera were used for this study. Frozen sections were made of this part. The method for demonstration of microglia of the silver carbonate techniques of del Rio Hortega[1] was used to stain some of the sections.

Histologic findings and discussion

The silver stains showed numerous microglia all through the inner layers of the posterior and intermediate retina of this case. The microglia of the retina are easily recognized by their small round nuclei and short branching pseudopodia-like processes (fig. 1). This shape of their protoplasm is known to be the expression of their motility.

All over the inner surface of the retina many of these microglia cells were seen in all phases of emigrating from the retina into the posterior chamber (figs. 1 to 4). The cellular shape of the microglia in this process of migration through the inner limiting membrane indicated that the openings through which these cells left the retina must be very small (figs. 2 and 4). Once in the vitreous space the migrating cells were seen to resume their rodlike or branching shape with the pseudopodia-like processes (figs. 5 and 6). Mitotic figures could be observed in this stage. This indicates that the retinal microg-

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Fig. 1 (Wolter). Two microglia cells (arrows) with short branching dark-staining cellular processes in the innermost layer of the retina. The microglia cell on the right side has extended two small processes through the inner limiting membrane into the posterior chamber. (Frozen section, Hortega stain for microglia, photomicrograph.)

Fig. 2 (Wolter). The lower half of the picture represents the innermost retina. A microglia cell (arrow) is seen migrating through the inner limiting membrane of the retina with a long extended process into the vitreous (upper half). (Frozen section, Hortega stain for microglia, photomicrograph.)

Fig. 3 (Wolter). A rodlike microglia cell (arrow) with delicate pseudopodialike processes migrating away from the retina (lower part of picture) into the vitreous exudate. (Frozen section, Hortega stain for microglia, photomicrograph.)

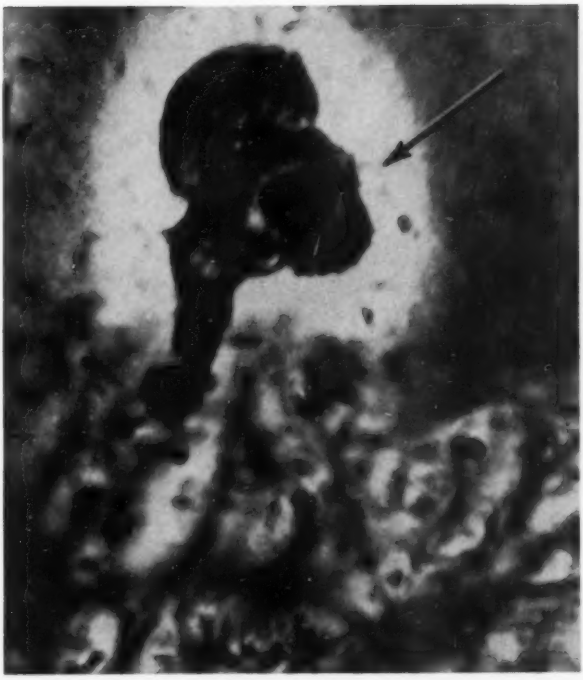

Fig. 4 (Wolter). A microglia cell (arrow) which still has one process in the inner limiting membrane of the retina is seen to migrate into the vitreous exudate. A halo of lighter stain is seen around the cell. (Frozen section, Hortega stain, photomicrograph.)

Fig. 5 (Wolter). A rod-shaped microglia (arrow) with a very distinct halo of lighter staining around it in the vitreous exudate. (Frozen section, Hortega stain for microglia, photomicrograph.)

lia was very active and actually proliferating in the vitreous.

Phagocytosis of exudates, cellular remnants, or erythrocytes are the typical functions of the microglia all through the central nervous system including the optic nerve and retina. All phases of the evolution of these cells in this process could also be observed in the vitreous of the present case. Many complicated protoplasmatic processes were seen to extend from the microglia into the vitreous exudate (fig. 6). It was interesting to observe in our slides that there always was a lighter staining zone around the macrophages in the darkstaining vitreous exudate (figs. 4 and 7). This halo around the macroglia is evidence of the proteolytic action of enzymes in the microglia. A protease is known to be present in microglia of other areas.[2]

Finally the phagocytosis was seen to have changed many of the microglia into large round cells (figs. 7 and 8). These stages of microglia after phagocytosis are well known

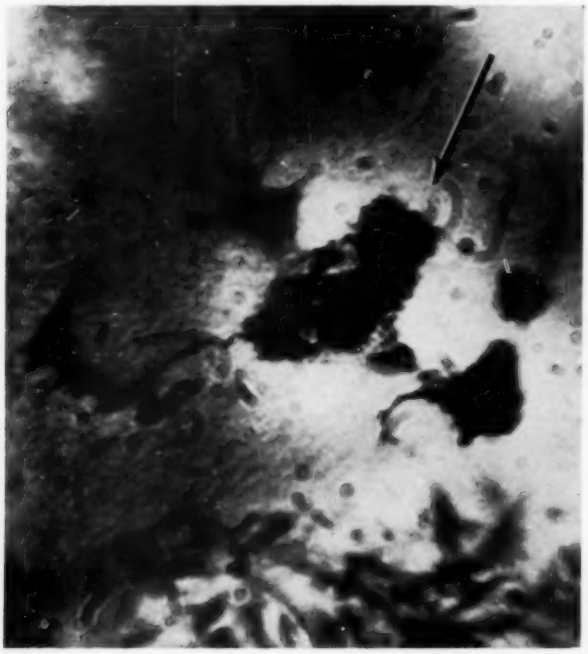

Fig. 6 (Wolter). A microglia cell (arrow) extending many pseudopodialike processes into the vitreous exudate in the process of phagocytosis. The innermost retina is seen in the lower part of the picture. (Frozen section, Hortega stain for microglia, photomicrograph.)

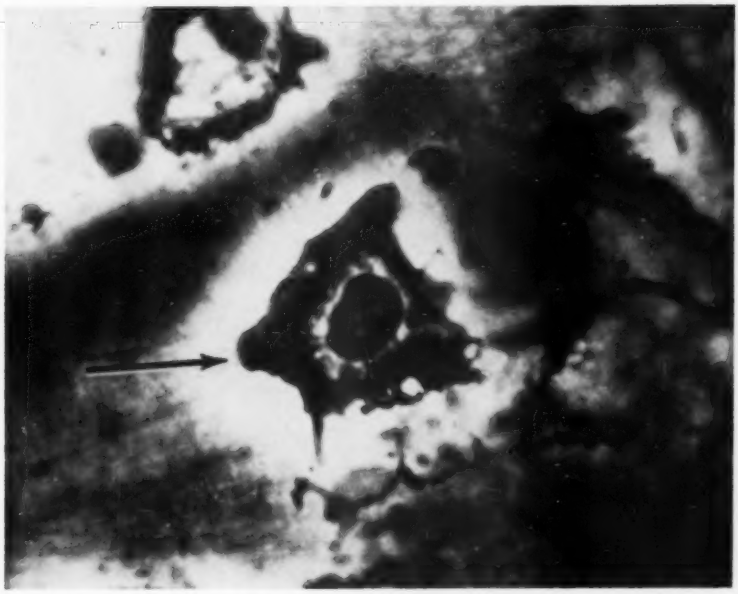

Fig. 7 (Wolter). A microglia cell (arrow) already shows some small vacuoles in protoplasm and has become larger in process of phagocytosis. A distinct halo is seen around cell. (Frozen section, Hortega stain for microglia, photomicrograph.)

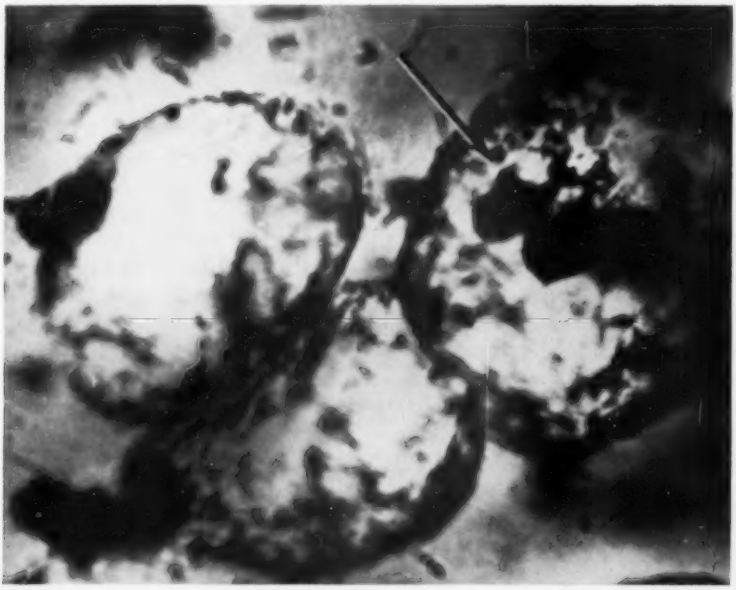

Fig. 8 (Wolter). Large microglia (gitter cells) after phagocytosis in the vitreous body. The cells are filled with vacuoles of phagocytized substance. Some of these cells have two nuclei (arrow). (Frozen section, Hortega stain for microglia, photomicrograph.)

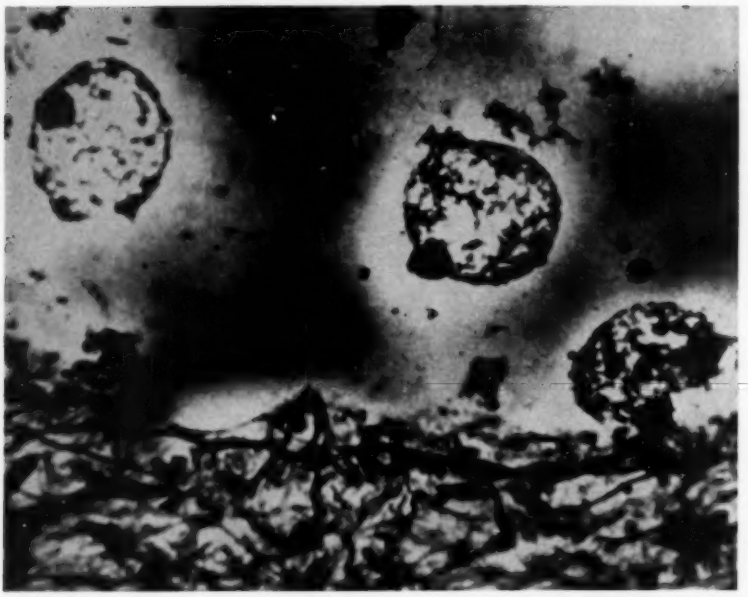

Fig. 9 (Wolter) Large gitter cells filled with vacuoles containing phagocytized substance close to the retina. The retina is visible in lower part of picture. (Frozen section, Hortega stain for microglia, photomicrograph.)

as granular compound corpuscles or gitter cells from general neuropathology. The small round nuclei are all that reminded of the original microglia. Some of these cells had two nuclei (fig. 8).

These large cells were found in all stages of migrating back to the inner retinal surface (figs. 9 and 10). Large accumulations of such round cells were seen on the retina especially in areas where there were superficial retinal blood vessels (fig. 11). I was unable to find in our slides—of this and other cases—any of these cells in the process of migrating back into the retina and to the wall of blood vessels. The microglia in their gitter cell-stage remained on the inner surface of the retina until degeneration of these cells occurred (fig. 12). Signs of this degeneration were loss of the cellular nuclei and membranes. Many cells were seen in their final stage of actually fading away. It seems that the cells with all their phagocytized contents then have become fluid that can reach the retinal blood vessels by diffusion.

It was interesting to observe that most macrophages of the vitreous in this case appeared to come from and to migrate back to the posterior and intermediate retina. In other cases it can be observed that similar cells may originate in the ciliary body. In cases of exudative retinal detachment microglia is often seen to invade not only the vitreous but also the exudate in the retroretinal space. This is most impressively seen in cases of Coats' disease. In the retroretinal space it is often quite difficult to differentiate the microglia of retinal origin from proliferating cells of the pigment epithelium. Both may contain pigment granules and look virtually alike.

Comments

The microglia represents the reticuloendothelial system of the central nervous system. Microglia cells are normally present in all organs and regions of the central nervous system but in each territory they are arranged according to the general architecture

Fig. 10 (Wolter). High-power view of a microglia cell after phagocytosis (gitter cell) in the vitreous close to the retina. (Frozen section, Hortega stain, photomicrograph.)

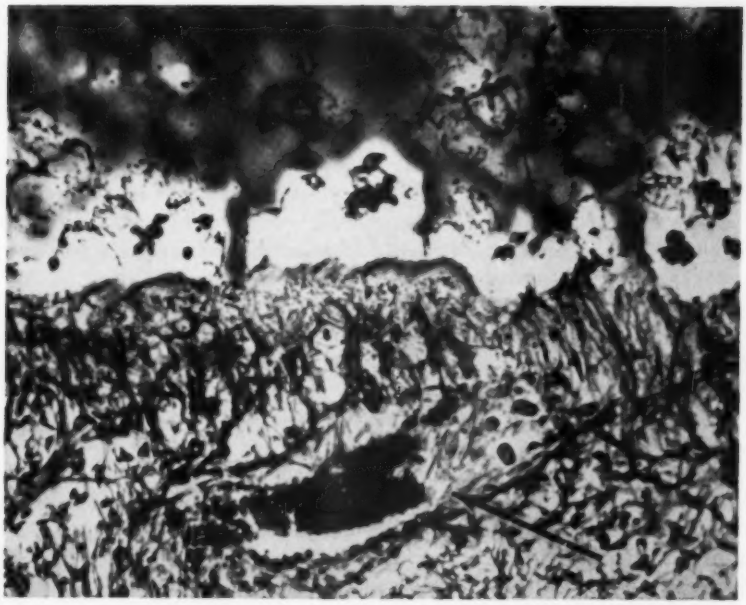

Fig. 11 (Wolter). Accumulation of numerous large microglia after phagocytosis (gitter cells) on the inner surface of an area of the retina where there is a blood vessel (arrow). The glial framework of the retina is not well stained with the method for microglia. (Frozen section, Hortega stain for microglia, photomicrograph.)

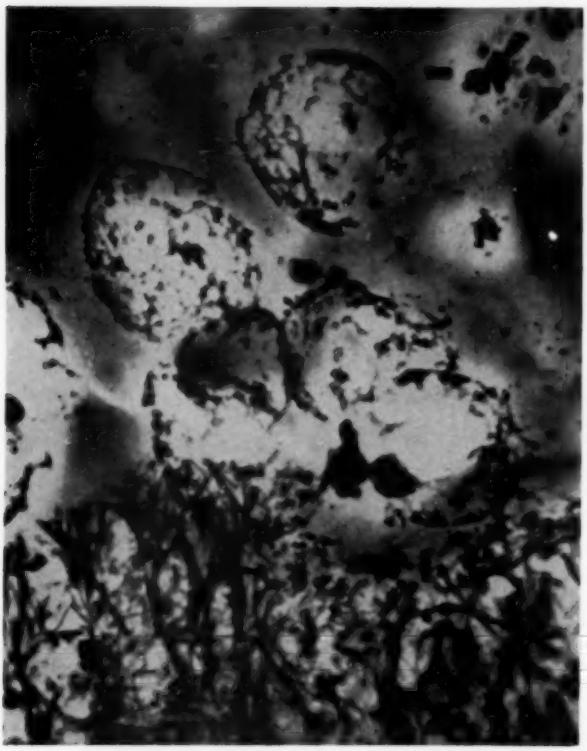

Fig. 12 (Wolter). Several degenerating microglia (gitter cells) on the inner surface of the retina. Nuclei and cell membranes are already partially lost. (Frozen section, Hortega stain for microglia, photomicrograph.)

and function. Microglia are mesodermal in origin. They were first described and fully understood in their nature and function by del Rio Hortega.[2] Therefore microglia is also known as Hortega cells.

The existence of microglia in the human optic nerve and retina was first demonstrated by Lopez Enriquez (1926)[3] and shortly after by Marchesani (1926).[4] Through the recent years extensive studies of the role of retinal microglia in human retinal pathology was published from this laboratory.[5-10]

The present demonstration shows that the function of the retinal microglia in the eye is not limited to the retina itself. The microglia may leave the retina and migrate into the posterior chamber to become what is well known as the macrophages of the vitreous.

The microglia in the vitreous behaves much like it does in all regions of the central nervous system. They migrate towards the pathologic involvement and phagocytize cellular debris, exudate, erythrocytes, or foreign substance. In this process the normally delicate microglia become large round cells filled with vacuoles containing phagocytized substance (gitter cells). In the central nervous system these cells then migrate back to blood vessels to deliver the substance to the blood stream. This, however, they do not seem to be able to do when they migrate into the vitreous of the eye. Here they accumulate after phagocytosis on the inner retinal surface as close as possible to retinal blood vessels. Having only a certain life time like all free moving mesodermal cells the gitter cells finally degenerate right in front of the retina. They are seen in all stages of fading away completely. This must mean that the structures of the cells as well as the phago-

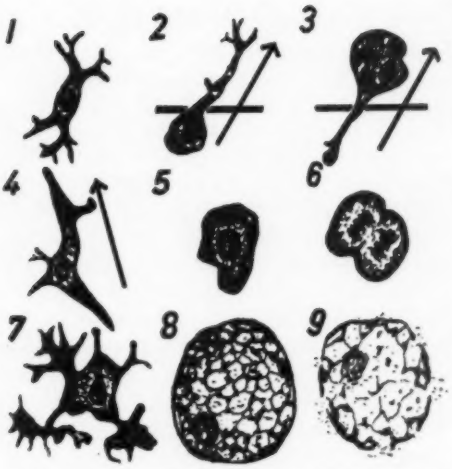

Fig. 13 (Wolter). Drawing to demonstrate the evolution of the microglia in the vitreous during phagocytosis: (1) normal microglia in the retina, (2) microglia migrating from retina through inner limiting membrane (horizontal line) into vitreous (direction of arrow), (3) microglia has almost left the retina and migrates in direction of arrow into vitreous, (4) rod-shaped migrating microglia in the vitreous, (5) microglia at rest in the vitreous, (6) mitosis in microglia in the vitreous (proliferation), (7) early phase of phagocytosis with many pseudopodialike processes extending into the substance to be phagocytized, (8) late stage of phagocytosis (gitter cell), and (9) final degeneration of gitter cell in the vitreous on the inner retinal surface.

cytized substances contained in it have become soluble and may reach the retinal blood vessels by diffusion through the inner limiting membrane and be thus removed from the vitreous.

Some of you may say that it is not right to call the macrophages of the vitreous microglia since they look and act much like histiocytes of mesodermal tissues and since cells just like them may be found in the anterior chamber and around the lens. However, these cells come from the retina and invade the secondary vitreous which is considered to have developed as a secretion product from the radial fibers of Müller. It seems logical, therefore, to call the macrophages of the vitreous just like those of the central nervous system microglia.

The existence of macrophages in the human vitreous under pathologic conditions is nothing new, of course. In this paper, however, we hope to have helped you to see where these cells come from, how they work and how they should be classified.

Summary

The reaction of microglia emigrating from the retina into the vitreous is demonstrated histologically in all its phases in the example of a case of extensive vitreous exudate caused by a retinal neoplasm.

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CENTRALLY FIXED FLICKER THRESHOLDS IN AMBLYOPIA*

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INTRODUCTION

Theories as to the etiology of amblyopia (also called amblyopia ex anopsia, strabismus amblyopia, and amblyopia without ophthalmoscopic signs) may roughly be divided into two groups depending upon whether the primary defect is postulated in the cerebral cortex[1] or in the retina.[2-5] Wald and Burian[1] who are among the most lucid advocates of the former position described measurements on five cases in whom the absolute threshold foveally and peripherally in both rods and cones, light adapted, and dark adapted were perfectly normal. They regard the dissociation of form vision and light perception as characteristic of the vision of amblyopic eyes.

Studies of the critical flicker frequency in amblyopia have also been made. Unfortunately, the available data in this regard are equivocal. Miles[6] repeated some of the experiments of Teräskeli[7] who found in the amblyopic eye a reduction of "the normal trend" for the critical flicker frequency in the center to be somewhat lower than in an area 10 degrees into the peripheral field. Miles obtained a similar result.

On the other hand Feinberg[8] found that in the normal eye the critical flicker frequency was highest at the center of the field but decreased the farther out into the peripheral field one moved. In amblyopia the critical flicker frequency in the peripheral field was frequently as high as that in the center because the central critical flicker frequency was reduced in the amblyopic eye.

Alpern and Spencer showed that the normal foval critical flicker frequency is the highest of all whenever the fluctuations in entrance pupil size are not allowed to influence the amount of light which reaches the retina but not otherwise. Feinberg also found that only the critical flicker frequency for the fovea was influenced by the amblyopia and the effect of the amblyopia was always a reduction in foveal critical flicker frequency. On the other hand both Teräskeli and Miles report cases in which the central critical flicker frequency was higher in the amblyopic eye than in the normal eye, other cases in which the reverse was true, and still other cases in which no difference between foveal critical flicker frequency could be found in the two eyes.

The discrepancy between these findings might be explained by the fact that the critical flicker frequency increases with the amount of light reaching the retina. Harms[10] has shown that the pupillomotor sensitivity of the center of the field is reduced in amblyopic eyes. With this decreased sensitivity a centrally fixed flicker stimulus would result in a wider pupil. This wider pupil would increase the retinal illuminance in the amblyopic eye. This would result in a tendency for the central critical flicker frequency in the normal and amblyopic eyes to be more nearly the same in the experiments of Teräskeli[7] and Miles[6] who made no attempt to control for fluctuations in pupil diameter. On the other hand Feinberg used a small artificial pupil in all of his experiments, and this source of error was thus avoided.

EXPERIMENTAL

Six young adult amblyopic patients were used in the present study. All of these patients were given a thorough ophthalmologic examination. A summary of the pertinent

* From the Department of Ophthalmology, University of Michigan. Assisted by Grant B-1578 from the National Institute of Neurological Diseases and Blindness of the United States Public Health Service, to Prof. Harold F. Falls for the psychophysical studies of ocular abnormalities. We gratefully acknowledge the advice of Dr. Falls and the technical assistance of Gilbert B. Lee.

ophthalmologic data is presented in the appendix.

The study was divided into two parts. In the first part measurements were made under conditions which were more or less typical for flicker perimetry and roughly correspond to conditions employed by Miles and to a less extent those of Teräskeli. In the second part measurements were made under more rigorously controlled laboratory conditions. Four of the six patients were subjects for both experiments. Of the other two patients, one was a subject only for the first experiment while the other was a subject only for the second. Thus, five subjects were studied in each experiment.

Experiment I

The standard flicker perimeter of the Eye Clinic at University Hospital was employed for this experiment. This apparatus has already been described.[11] It consists of a neon glow lamp which can be pulsed at various rates by a General Radio Company Strobotac. This lamp was fixated centrally in an otherwise darkened field. No other attempt was made to control adaptation in these experiments. Measurements were made alternately of central critical flicker frequency first of the normal then of the amblyopic eye.

Measurements were made by starting with a light pulsing above the critical flicker frequency, and reducing its rate of alternation until the first appearance of flicker; this point was bracketed several times but the final threshold was at the point of the first appearance of flicker. In a rather detailed study of the psychophysical problems of determinations of critical flicker frequency Maheneke[12] has shown that this method gives very reliable measurements. Measurements made in this way compare well with those obtained by the constant stimulus procedure.

A series of measurements in two separate sessions were obtained of the critical flicker frequency both with and without a small (1.0 mm. in diameter) artificial pupil before the patient's eye. All measurements were made monocularly, the other eye was occluded during the testing.

The results of this experiment are summarized in Table 1. When no artificial pupil was employed in any given subject the measurements were quite varied. Hence, the critical flicker frequency for the amblyopic eye after any given measurement, taken immediately before or after might be higher, equal to, or lower than that of the normal eye. On the average no significant difference was obtained between the critical flicker frequency in the normal and that in the amblyopic eye. On the other hand when a 1.0 mm. artificial pupil was centered in front of the eye the critical flicker frequency was consistently (and, using the simple sign test, significantly) lower than the critical flicker frequency of the normal eye. All of these findings were essentially the same in each of

TABLE 1

Clinical measurements of flicker thresholds with and without artificial pupil in normal and amblyopic eyes

Subj.	Without Artificial Pupil					With Artificial Pupil				
	N.	Mean C.F.F. Normal Eye	Mean C.F.F. Amblyopic Eye	Diff.	P.	N.	Mean C.F.F. Normal Eye	Mean C.F.F. Amblyopic Eye	Diff.	P.
P. S.	16	41.94	41.12	0.82	0.388	16	33.25	30.81	2.44	0.001
R. M.	31	45.64	45.41	0.23	0.664	33	41.39	39.87	1.52	0.001
P. K.	40	47.77	47.14	0.63	0.373	40	37.55	35.48	2.07	0.001
A. M.	29	46.48	46.10	0.38	0.454	29	36.48	31.97	4.51	0.001
M. A.	30	42.70	42.46	0.24	0.360	29	37.37	36.55	0.82	0.012

the subjects studied so that while individual differences in the absolute value for the critical flicker frequency were found the trends were always identical.

These results strongly suggest that if one avoids the contaminating influence of decreased pupillomotor sensitivity in amblyopia (Harms) the critical flicker frequency for the center of the field is always lower in the amblyopic eye than in its normal fellow. It is necessary, however, to exert a note of caution since the measurements just reported were all made at a single intensity of the flickering stimulus and it is not possible to generalize these findings to the entire gamut of intensities.

A number of other complications are, moreover, present with the apparatus employed for the measurements reported in Table 1. Perhaps the most important one is the appearance of flickering stimulus in a totally dark field. Thus, when such measurements are made it is subject to the probability that small eye movements will present the flickering stimulus to a region of the retina previously stimulated only by darkness. Furthermore, it is difficult if not impossible, with this form of the apparatus to exert an adequate control over the adaptation state of the eye. The influence of adaptation on critical flicker frequency measurements is well known.[13]

Still a third complication is the fact that frequency variation in the strobotac is achieved by variation of the duration of the off phase of the flickering cycle. Hence, different critical flicker frequency values are represented by different on/off ratios and the physiological interpretation of the data becomes rather complicated.

For these reasons a second series of experiments were carried out in which factors known to influence flicker thresholds were controlled as carefully as possible.

Experiment II

The apparatus of this experiment is illustrated in Figure 1. The source S_1 was an automobile headlamp operated at 6.0 v., 2.5 amp. of direct current which was maintained steady by a battery eliminator connected in parallel with two 6.0-v. automobile batteries. The current to the lamp was monitored by a sensitive ammeter and was always maintained at a constant value by adjustments, when necessary, of the resistance in a rheostat which was connected in series with the lamp. Light from the filament of the source was focused on a small 2 mm. aperture, and immediately after emerging from this

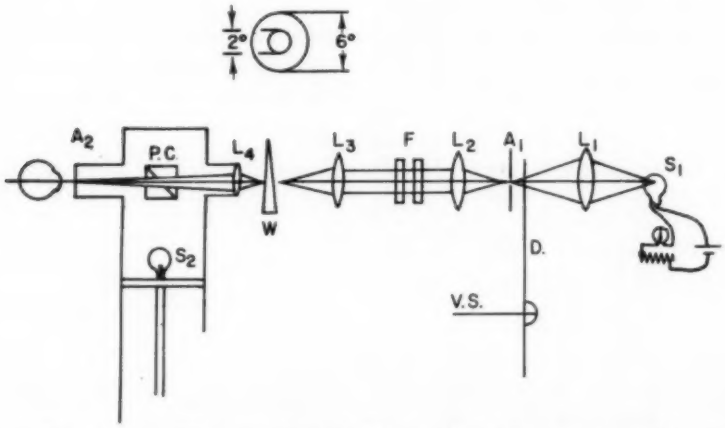

Fig. 1 (Alpern, Flitman and Joseph). Line drawing of the apparatus used in the second series of experiments.

aperture was interrupted by a sectored disc (on/off ratio = 1.0) which was mounted to a variable speed friction drive apparatus driven by a constant speed motor. The rate of rotation of this disc could be determined almost immediately by a strobotac. An image of the aperture A_1 was formed at aperture A_2 (a small 1.4-mm. aperture which was immediately in front of the subject's eye). This provided a Maxwellian view of the flickering stimulus of high intensity. Wratten neutral density (No. 96) filters could be placed in the beam and thus vary the luminance of the stimulus. The aperture A_3 was mounted in the eyepiece of a Macbeth Illuminometer and this provided a six-degree surround which was maintained equal to that of the Talbot luminance of the flickering light as long as this latter was equal to or less than 25 ft.-L. (for higher levels the surround was maintained at 25 ft.-L.). A variable neutral density wedge (W) was also mounted in the beam.

The subject was first allowed to remain in the dark for 30 minutes before any measurements were made. He then carefully fixated the center of the field monocularly at the lowest level (Talbot retinal illuminance = 0.02 trolands) and a measurement of critical flicker frequency was made (using the same psychophysical procedure described in Experiment I) as quickly as possible. The observer then shifted positions so that his other eye then fixated the center of the field and a second measurement was made. The entire process was then repeated. After this the light level was increased by one third of a log step (to 0.0706 trolands). The observer first adjusted the Macbeth Illuminometer so that the surround luminance was equated to the Talbot luminance of the flickering field and then adapted for a few moments to this new light level. Following this the entire process was repeated in exactly the same way as that used at the lower level. In this way critical flicker frequency was determined alternately for each eye over a gamut of intensities extending to almost seven log units in one-third log steps. The entire process was repeated separate days in all but one case for a total of three times and for P.S. for a total of two times.

The results of these experiments on each eye of each observer are summarized in Figure 2. In the figure the ordinates are values of critical flicker frequency and the abscissae are values of the logarithm of the Talbot retinal illuminance in trolands. The data for observer M.A. are properly positioned on the graphy while those for R.M. are shifted 2.5, those for M.D. are shifted 5.0, those for P.S. are shifted 7.5, and those for A.M. are shifted 10 log units to the right along the abscissa.

It is clear from the results in this figure that the same general equation describes the relation between the critical flicker frequency and the intensity of the flickering stimulus for each observer both in the normal and the amblyopic eye. Over a wide range of luminances the Ferry-Porter equation, that is

$$\text{c.f.f.} = k \log I + b, \qquad (1)$$

adequately describes the data. In this equation k and b are constants whose numerical values depend upon the subject and the units employed, and I is the Talbot retinal illuminance. At both extremely high and extremely low light levels the Ferry-Porter equation is inadequate. In the former case it underestimates and in the latter case it overestimates the critical flicker frequency. These results also show that while the critical flicker frequency for the amblyopic eye follows the same general trend as that of the normal eye the constants of the Ferry-Porter equation in the two eyes of any given observer are usually slightly different. This result is emphasized in Table 2 which presents the constants k and b obtained for Eq. (1) in the normal and amblyopic eyes of each observer.

The value of k in Eq. (1) represents the rate of change of critical flicker frequency with change in the logarithm of retinal illuminance. It is seen from the table that the

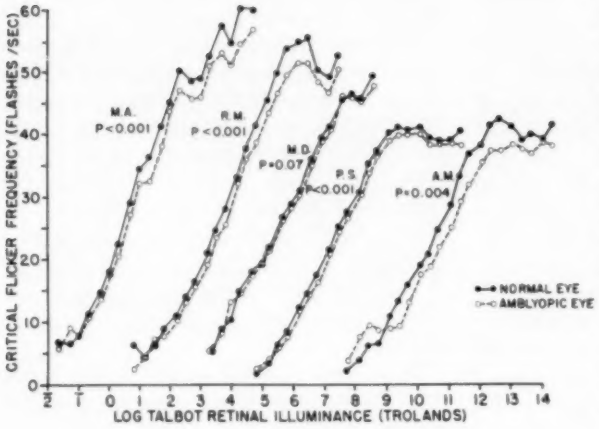

Fig. 2 (Alpern, Flitman and Joseph). The relation of critical flicker frequency and intensity for the center of the visual field in the normal (closed circles) and amblyopic (open circles) eyes of five subjects. The curves for M.A. are properly positioned on the graph, while those for the other subjects are shifted to the right on the abscissa axis: R.M. 2.5 log units; M.D. 5 log units; P.S. 7.5 log units and A.M. 10 log units. The statistical statements made on each set of curves are the possibility that the discrepancy observed could have occurred by chance based on a nonparametric (simple sign) test. It should be emphasized that these statistics were based on the data from the entire gamut of intensities, and are consequently conservative estimates of the significance of the difference in critical flicker frequency values in normal and amblyopic eyes for the intensities for which differences were found (that is, intensities above 0.2 trolands).

value of k is very slightly smaller in the amblyopic eye than in the normal eye for each of the observers. The value of b represents the critical flicker frequency value when logarithm of intensity is equal to 0. Again, while individual differences in observers are apparent the value of b is larger in the normal eye than in the amblyopic eye in each case.

The differences in the constants of the Ferry-Porter equation in the normal and amblyopic eyes are small but in both cases the probability that such differences could have occurred by chance is very slight ($p = 0.031$; simple sign test). This analysis shows that at any given intensity the critical flicker frequency is slightly smaller in the amblyopic eye than in its normal fellow for the center of the visual field. This statement is true over the range of intensities for which the relation between critical flicker frequency and logarithm of intensity is linear.

TABLE 2

CONSTANTS OF THE FERRY-PORTER EQUATION IN NORMAL AND AMBLYOPIC EYES

Subj.	(c.f.f. = k log I + b) Normal Eyes		Amblyopic Eyes	
	k	b	k	b
M. A.	13.20	19.3	13.05	16.9
R. M.	12.20	13.2	11.85	10.9
M. D.	9.20	21.0	8.70	20.4
P. S.	9.27	24.9	9.20	23.7
A. M.	9.35	17.9	9.10	14.9
	10.64	19.26	10.35	17.36

Examination of the data in Figure 2 shows that the statement is also true for all higher intensities as well. As a matter of fact, due to the slightly smaller slope of the lines for the amblyopic eyes the effect of increasing intensity is to increase the disparity in critical flicker frequency between the normal and amblyopic eyes. On the other hand when the intensity is so low that the Ferry-Porter equation begins to underpredict the critical flicker frequency then the trend is less obvious. Four of the cases show little if any difference in the critical flicker frequency of the normal and the amblyopic eye at these low levels. In one case (A.M.) the critical flicker frequency in the amblyopic eye at these low levels is higher than in the normal eye.

Discussion

The results of these experiments emphasize that when fluctuations in pupil diameter are prevented from interfering with the amount of light which reaches the retina the critical flicker frequency is higher in the normal eye than in the amblyopic eye in the center of the visual field for all levels higher than 0.2 trolands. Reports of previous investigators of different results can be attributed to their failure to control fluctuations of pupil size and the fact that the pupillomotor sensitivity of the center of the field of the amblyopic eye is reduced compared to that of its normal fellow (Harms).

Since the critical flicker frequency in the center of the visual field is reduced in amblyopia it seemed important to compare this effect with the reduction of the central visual acuity which is the major characteristic of this entity. In order to do this, measurements of central acuity at various levels of illuminance were made on three of the subjects (who were still available for testing).

The test chart was an ophthalmologic acuity chart with variable sizes of letters. It was illuminated by a 300-watt tungsten filament lamp in a 35 mm. slide projector. Light level was varied by Wratten No. 96 neutral density filters in front of the projector and/or in front of the eye. Stray light in the room was carefully screened from entering the subject's eyes.

The subject was dark adapted for 30 minutes and then viewed the test chart at the lowest light level through a 2.0 mm. in diameter artificial pupil. The other eye was occluded. After adapting to the light level he walked toward the chart until he could just read a designated size letter and the distance of his eye from the chart was recorded together with the letter size. Two such measurements were made in succession. The occluder patch and the artificial pupil were then interchanged and two similar measurements were made on the other eye. The level of light was increased by one half log step and, after the subject allowed his eyes to adapt to this new level, the procedure was repeated. In this way measurements were made over the entire range of intensities from the lowest to the highest.

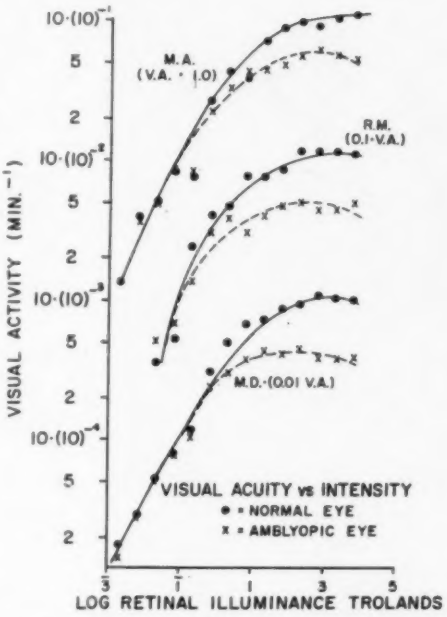

Fig. 3 (Alpern, Flitman and Joseph). The relation of visual acuity and intensity for the center of the visual field in the normal (circles) and amblyopic (x's) eyes of three subjects. The data for M.A. are properly positioned on the graph; those for R.M. are shifted down on the ordinate scale one logarithmic unit while those for M.D. are shifted down on the ordinate scale two log units.

The results of these experiments are illustrated in Figure 3 which shows the logarithm of the visual acuity as a function of the logarithm of retinal illuminance. At low levels the visual acuity in the normal and amblyopic eye were essentially the same. Increasing the light level was associated with an increase in the visual acuity in both the normal eye and the amblyopic eye. Over a range of intensities the rate of change of acuity with illuminance in the two eyes was not very different. At levels of illuminance (around 0.1 troland) the visual acuity of the normal eye became a little better than that of the amblyopic eye. While further in-

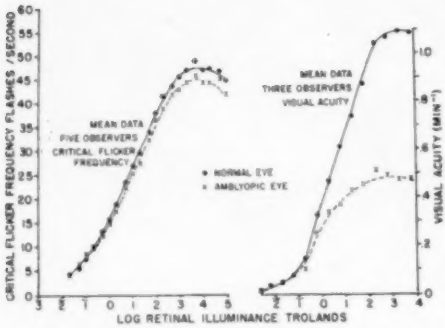

Fig. 4 (Alpern, Flitman and Joseph). Mean data of critical flicker frequency and visual acuity as functions of intensity for the normal (circles) and amblyopic (x's) eyes.

crease in intensity was associated with an increase in acuity in both eyes the disparity in the acuity of the two eyes was accentuated by the higher light levels.[14, 15]

Figure 4 shows a comparison of the mean data of flicker and acuity in the normal and amblyopic eyes as functions of intensity. The acuity curve shows the greater distortion in amblyopia than does the flicker curve. Nevertheless, the two functions show quite similar impairment with this effect. The reduction of the critical flicker frequency in amblyopia, just like the reduction of visual acuity, cannot be described as a simple shift of the data on the intensity axis as one might anticipate if the defect were analogous to looking through a neutral filter with the amblyopic eye. Nor on the other hand was the effect of amblyopia to depress the sensitivity of the eye uniformly at all luminance levels. On the contrary, the sensitivity of the center of the field at low levels is remarkably similar in normal and amblyopic eyes. Wald and Burian[1] found the absolute threshold of the fovea unaltered in amblyopic eyes, and it was for essentially this reason that they described amblyopia as resulting in the dissociation of form vision and light perception. Our experiments suggest, however, that a more exact description would be that amblyopia results in an impairment of visual functioning (both acuity and flicker discrimination) at moderate and high levels of retinal illuminance without any impairment of visual function at low levels at all. Similar results have been obtained for brightness discrimination[2] and there seems no reason to doubt the generality of this conclusion.

The equality of the sensitivities of the two eyes at low light levels which gradually gives way to a greater and greater disparity in sensitivity, as the intensity is increased, would not be anticipated a priori if amblyopia were either a reduction in the rate of resynthesis of pigments in,[2] or a tilting of,[3, 4] foveal photoreceptors. On the other hand, it is now realized that the light sense and form vision are not as obviously dissociated in amblyopia as Wald and Burian suggest in their "cortical" theory of amblyopia. It is evident that any conclusive decision as to the location of the primary defect in amblyopia is still premature.

How can this loss of sensitivity of the amblyopic eye at high light levels be explained? While it is not possible to be explicit about this at the present time at least two possibilities can be considered. In the first place it might be imagined that a few rods might have intruded into the central two-degree area covered by the retinal image of the flickering stimulus in the amblyopic eye. The suggestion is brought to mind by the double curve relating flicker and intensity in the amblyopic eye of one of the subjects (A.M.) Such a curve is characteristic of flicker data when the tested retinal area contains both rods and cones.

When the tested retinal area contains only cones a single monotonic curve can be drawn through the data and this was the usual result of the present experiments. However, the curves in the amblyopic eyes of the other observers might be a milder manifestation of the same defect. Another explanation for the same result would be that fixation with the amblyopic eye is accomplished with a region of the retina just slightly eccentric

to the center of the fovea (but still well within the part of the retina stimulated by the central part of the image of the test patch). In fact measurements of the precision of central fixation using the entopic perception of the macula[16] revealed a slight eccentric fixation in the amblyopic eyes of two of the subjects (21′ in M.A.; 18′ in R.M.) and centered fixation in their normal eyes. (In the only other subject available for this measurement (M.D.) a slight eccentric fixation of exactly the same magnitude 20′ and direction was obtained in both the normal and the amblyopic eye.) This notion is in good agreement with a number of clinical[17] and laboratory measurements on amblyopic eyes.[12, 19]

On the other hand, any crucial testing of the validity of these speculations and their relative merits would require a rather more extensive knowledge of the characteristics of the chromatic and achromatic senses in amblyopic as compared to normal eyes than is yet at hand. In view of this fact it seems prudent to postpone any thorough discussion of these problems until studies currently underway in this laboratory (and perhaps elsewhere) are concluded.

Summary

When the fluctuations of pupil diameter are permitted to influence the amount of light reaching the retina then there is no obvious difference in the critical flicker frequency in the center of the field for the normal and amblyopic eyes. When, however, such fluctuations of retinal illuminance with pupil diameter are obviated with an artificial pupil then the critical flicker frequency for the center of the field is lower in the amblyopic eye than in the normal eye. The magnitude of the difference depends upon the amount of retinal illuminance, being zero at very low light levels but gradually increasing as retinal illuminance increases. The relation between critical flicker frequency and intensity in the two eyes in amblyopia is quite similar to the relation of acuity and intensity, but the magnitude of the discrepancy in the latter case is, of course, more pronounced.

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Appendix

Summary from the records of the subjects of the present experiments:

R.M., 27-year-old man, with poor vision and right esotropia since the age of two years. Treatment of patching and exercise but no surgery. Refraction (cycloplegia) R.E. −2.50 sphere; L.E. −3.75 sphere; visual acuity with correction R.E. 20/30; L.E. 20/15. Patient has a small angle right esotropia with a full range of extraocular movement. Slitlamp and ophthalmoscopic examinations of each eye were normal.

M.D., 36-year-old woman, who first noticed poor vision in L.E. 10 years ago. The eyes are straight; the extraocular movements are full; PCB is good. Refraction (cycloplegic) R.E., +3.25D. sph. ⊃ +0.5D. cyl. ax. 30°; L.E., +4.0D. sph. ⊃ +1.25D. cyl. ax. 145°; visual acuity with correction 20/15 and Jaeger 0 R.E.; and 20/40 Jaeger 4 L.E. Ophthalmoscopic and slitlamp examinations were normal.

P.S., 25-year-old man, who has always had poor vision in his left eye. Treatment by patching the right eye but no surgery. Refraction (cycloplegic) R.E. −1.75D. sph., L.E. −1.25D. sph. ⊃ +0.5.D. cyl. ax. 165°. Visual acuity with correction R.E. 20/15 and Jaeger 0; L.E. 20/30 Jaeger 4. Examination showed normal extraocular movements with a remote PCB. There was 20Δ exotropia for distance and 5Δ exophoria for near. No stereopsis. Slitlamp examination was normal. Ophthalmoscopic examination R.E. was normal; L.E. showed a blurring of the disc and situs inversus vasorum. Visual field examination was normal.

A.M., 24-year-old man, who first noticed poor vision in the right eye eight years ago while shooting a gun. No history of strabismus. Refraction (cycloplegic) R.E. +3.75 sphere; L.E. −0.50 sphere, +0.25 cylinder axis 155. Visual acuity with correction R.E. 20/200—L.E. 20/25 Jaeger 0. Examination showed the eyes straight to cover; normal extraocular movements with a good PCB. Ophthalmoscopic and slitlamp examinations were normal in each eye.

M.A., 38-year-old man, who developed an alternating esotropia at age of three years following measles. Treatment consisted of glasses and orthoptics but no surgery. Refraction (cycloplegia) R.E. +3.25 sphere +0.75 cylinder axis 100; L.E. +3.00 sphere +1.50 cylinder axis 94. Visual acuity with correction R.E. 20/15 and Jaeger 0; L.E. 20/25 and Jaeger 0. Examination revealed a full range of extraocular movements with a good PCB an alternating esotropia of 12Δ at far and 18Δ at near with predominantly right fixing eye. Ophthalmoscopic examination of each eye was normal.

P.K., 19-year-old woman, with a left esotropia since the age of six years. This was treated with glasses and orthoptics but no surgery. Refraction (cycloplegia) R.E. +1.75D. sph. ⊃ +2.0D. cyl. ax. 90°; L.E., +5.75D. sph. ⊃ +2.0D. cyl. ax. 90°. Visual acuity with correction R.E. 20/25 Jaeger 0; L.E. 20/20 Jaeger 1. There was a left esotropia of 30Δ far and near with glasses. Extraocular movements were full and PCB good. Ophthalmoscopic and slit lamp examinations were normal.

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THE USE OF DOMESTIC ANIMALS FOR EXPERIMENTAL OPHTHALMOLOGY*

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There is a growing consciousness that the ocular anatomy of the animals used in experimental ophthalmology is sufficiently different from that of man to make the results of some experiments quite inadequate as a basis for application to human subjects or patients. It is also becoming evident as a result of our extensive anatomic dissections that there may be animals which have hitherto been ignored but which are easily available for special kinds of experiment.

The anatomic differences between the easily available domestic animals and man can perhaps be divided into three categories:

1. There are those which can be used for specific experiments that may reveal useful information applicable to the human ocular system.

* From the Department of Ophthalmology and the Institute for Research in Vision, Ohio State University. Presented at the meeting of the East-Central section, January, 1960.

2. There are those which suggest that certain kinds of experiment on any of the animals could never be related to the human system.

3. There are features which give no information at present, but which appear to deserve investigation, and which might broaden our knowledge of human ocular function.

Dealing with those features which would come in the first category we find that the sheep is unique in that it should be possible to attack the circulation of the lacrimal gland of this animal without entering the orbit. The lacrimal artery is a branch of the superficial temporal artery and branches from it also pass beyond the gland to give rise to some of the anterior ciliary arteries and the lateral conjunctival vessels (the medial part of the conjunctival loop is derived from the malaris artery).

It should be possible to observe the modified function or the degeneration of the lacrimal gland with an arterial block, and in turn the effect of this on the cornea and conjunctiva. The effects of bacterial invasion in the absence of lacrimation could perhaps be studied in this animal.

A slightly different approach to this experiment could also be used on the rabbit because this animal has a very large lacrimal gland which almost completely surrounds the globe. Its vascular supply reaches it by three distinct routes, and it would be interesting to evaluate the results of reducing lacrimal function by selective interference with these arteries.

Another unique and perhaps useful feature is found in the hog. A small sensory nerve path from the superior oblique muscle to the frontal nerve, and from the superior and medial recti and the retractor bulbi muscle to the nasociliary nerve may be traced without great difficulty in this animal. Two or three fibers also pass from the retractor bulbi to one of the long ciliary nerves. But perhaps most important from our point of view is the fact that a branch

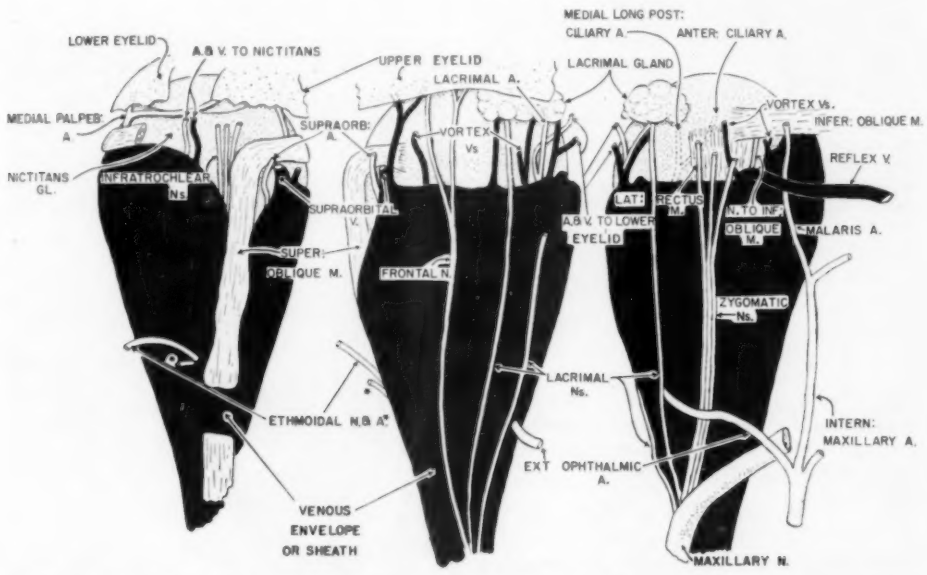

Fig. 1 (Prince and Ruskell). In the hog, the orbital contents are virtually enclosed within a venous envelope or sheath. The only point of ingress is anteriorly or where the superior oblique muscle passes through it.

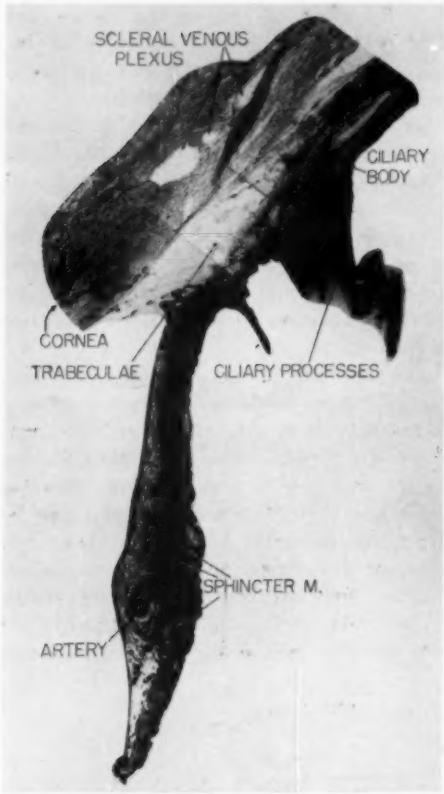

Fig. 2 (Prince and Ruskell). The aqueous drainage of the dog is through a scleral venous plexus. This illustration shows the iris and corneal angle. Other domestic animals have similar drainage systems.

from the motor nerve that serves the inferior oblique muscle receives a group of very fine nerves, evidently sensory, from the lateral rectus muscle. This branch passes out of the orbit to join the maxillary nerve just anterior to the foramen orbitorotundum. This again means that we have some limited access to a system without entering the orbit.

Only by an anterior approach can the orbit of the hog be entered, because most of its orbital contents are enclosed within a venous sheath or envelope except where it parts to reveal the superior oblique muscle. Any penetration of this sheath would prove irremediable because of hemorrhage.

In the second category covering anatomic features of domestic animals which are different from their counterparts in man, we have one very striking example in the source of retinal circulation. In man, in whom it derives from the ophthalmic artery, there is some dispute regarding possible anastomoses between the central retinal artery and the uveal blood supply (see François and Neetens,[3] Wybar[4]) but it is apparent that there are no major anastomoses between these systems. In the dog, cat, and rabbit however, much used animals for ophthalmic experiments, the retinal vascularization is derived from the ciliary vascular system. In most of the animals we have studied the retinal arteries all branch from posterior ciliary arteries so that there is no possible way of iso-

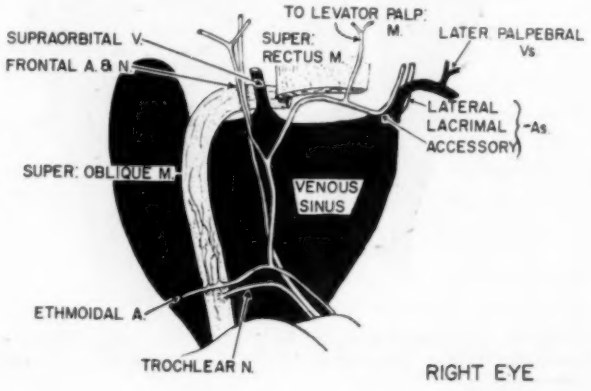

Fig. 3 (Prince and Ruskell). The venous sheath of the rabbit leaves the superior oblique muscle outside it but encloses all the other ocular adnexa.

lating the retinal system from the choroidal posterior to the lamina cribrosa.

In ophthalmologic experiments with animals, although the results may not necessarily be intended for application to man, a precise knowledge of the ocular anatomy is nevertheless essential in order to interpret these results adequately.

In all of the domestic animals we have dissected the ciliary, and consequently the retinal vessels have two origins. Their main blood flow is from the external ophthalmic artery which is an indirect branch of the external carotid, but a subsidiary source is via the internal ophthalmic artery which is a branch of the internal carotid artery. In their experiments to determine the retinal circulation time by injection of fluorescein into the splenic vein, Flocks, Miller, and Chao[1,2] found that their "end-points," that is, the moment of entry of fluorescein into and its exit from the eye, were not discrete. In an earlier experiment they had injected trypan blue into the internal carotid artery and found clearer "end-points." This difference was probably, in part at least, due to their selective use of only one of the blood routes to the retina (via the internal ophthalmic artery) in the latter case but both routes in the former (via the internal and external ophthalmic arteries).

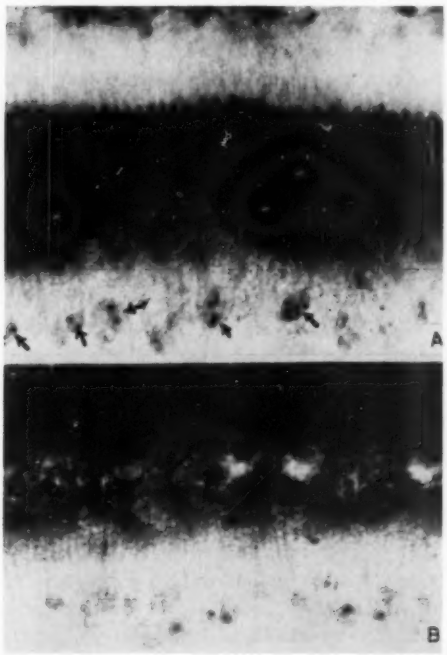

Fig. 4 (Prince and Ruskell). The rabbit's retina contains multinucleolated ganglion cells (A), and giant bipolar cells (B). See arrows in both pictures.

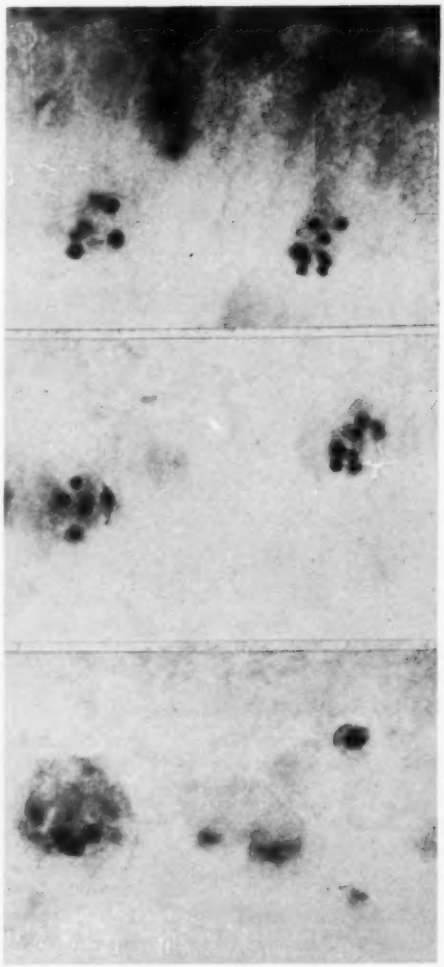

Fig. 5 (Prince and Ruskell). The multinucleolated ganglion cells under higher magnification. Sometimes there are up to 10 nucleoli.

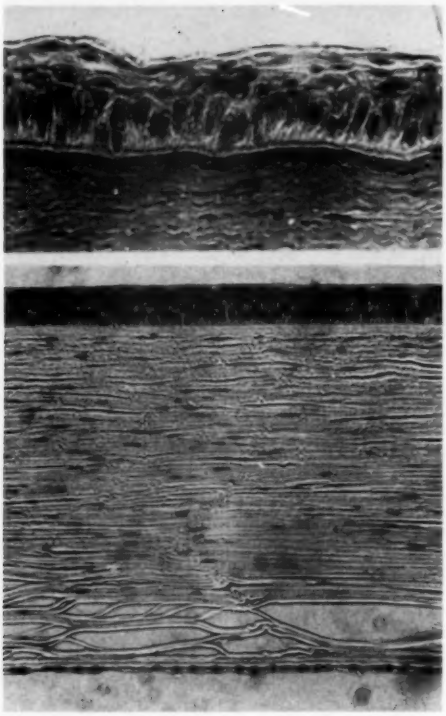

Fig. 6 (Prince and Ruskell). At the top is a section showing the rabbit Bowman's membrane which is no more than two microns thick. At the bottom is a section through a human retina in which this membrane is usually about 12 microns thick.

A second important area in which these animals differ from man is in aqueous drainage. This is apparently much more extensive in the animals, in fact a canal of Schlemm does not appear to exist as such in some of them. Instead, there is a system of vessels known as a "scleral venous plexus." In the dog this can be about four vessels of up to 60 microns in diameter and maybe three larger ones up to 180 microns. None of them occupy the precise position of the canal of Schlemm in man but they are served by smaller vessels from the trabecular region from which they are displaced by almost half the thickness of the sclera.

In the cat the same system is sometimes even more extensive, often as many as nine vessels, the larger three of which may be up to 200 microns in diameter, and the smaller ones from 40 to 70 microns. They accept smaller vessels down to eight microns in diameter. It is usually possible to find some blood in the larger vessels, but the smaller ones seem free from it.

Our studies are not sufficiently extensive to enable us to comment on the use of experimental animals in the determination of the rate of aqueous outflow from the eye or the nature and rate of transmission of fluids through the cornea. We feel that a more extensive knowledge of the anatomy of the structures of the filtration angle would be valuable and we hope to pursue work of this nature in the future.

A curious but obviously important difference between some of the domestic animals and man is the presence in the former of vascular retes and extensive venous plexuses within the orbit. The cat has a large intraorbital vascular rete which has a considerable extraorbital extension and in which most of the ocular blood vessels have their origin. The comparative vascular system of the dog is much less complex. The venous sheath of the rabbit surrounds the intraorbital tissues and any attempted surgery outside Tenon's capsule may produce extensive and probably irremediable haemorrhage.

Sometimes these venous reservoirs or envelopes almost completely enclose the orbital contents. As already mentioned, the only way into the orbit of the hog, other than from the frontal aspect is through a small aperture in this venous sheath where the superior oblique muscle rises to pass through the trochlear and turn toward its insertion. The rabbit has much the same kind of pattern, and because most of the anterior veins of the orbit drain into and out of this reservoir, as does the main posterior drainage channel from the orbit, it is obvious that it is exceedingly vulnerable.

The rabbit, especially the white rabbit, also falls into the third category, in which

there are features which deserve further investigation. For instance, the white rabbit's retina deserves some careful consideration. In the inner nuclear layer there are some very large cells, perhaps brush bipolars, but more logically giant horizontal cells. They are about 22 microns in diameter, and their nuclei eight microns. They seem to occur in their greatest numbers in the region where ganglion cells are scarce, and where there are the greatest numbers of outer nuclei.

Another interesting feature of the retina of the white rabbit is the presence of a number of clearly multinucleolated cells in the ganglion cell layer, where there are also some obvious glial elements. The number of nucleoli in these cells varies from two to 10, usually more than the number encountered in neural cells. The ganglion cells vary in size as do those of many other animals. There is one kind which range from 12 to 16 microns in diameter, another which is about 20 microns, and in the New Zealand rabbit at least, a giant ganglion cell from 27 to 36 microns in diameter.

When considering the rabbit, it is also necessary for us to remember that the two orbits have one common optic foramen, and that the medial recti have one common origin. The common optic foramen also carries an anastomosing artery between the extensions of the internal ophthalmic arteries of the two orbits. It is important to settle a controversy regarding Bowman's membrane in the rabbit. It has been stated that this membrane does not exist in this animal, but we have definitely found one. It is thin, probably never more than two microns thick as against 12 microns in man, but it is definitely there.

Bowman's membrane is always difficult to see in the domestic animals, often being little more than 10 percent of the thickness of that of man. This may disguise something which may be of considerable value to our knowledge of this membrane in man, and comparative studies may be desirable.

Summary

This paper, which results from work carried out for the preparation of a book entitled *Anatomy and Histology of the Eye and Orbit in Domestic Animals,* now in print, emphasizes the necessity for a greater knowledge of the ocular anatomy of animals used in ophthalmologic experiments the results of which may need to be related to man. The domestic animals are divided into three categories:

1. Those which can be used for specific experiments that may reveal useful information applicable to the human ocular system.

2. Those which suggest that certain kinds of experiment on any of the animals could never be related to the human system.

3. Those features which give no information at present, but which appear to deserve investigation, and which might broaden our knowledge of human ocular function.

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AUTONOMICLIKE EFFECTS OF OCULAR EXTRACTS*

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Extensive studies by Ambache[1,2] have resulted in the preparation and purification of a relatively specific smooth muscle-stimulating and pupil-constricting substance in extracts of iris tissue from various species. This substance has been named "irin." The chemical properties of irin seem to identify it closely with ricinoleic acid. Ambache reports, also, an irinlike substance in the conjunctiva and aqueous humor of rabbits following paracentesis.[3]

There are many obvious implications associated with the finding of autonomic-mimetic drugs in ocular tissue concerning not only the accommodation and pupillary reflexes but, also, aqueous humor dynamics. These drugs could stimulate intraocular muscle systems directly and could help regulate, also, patency of intraocular vessels concerned with both aqueous formation and aqueous drainage. It seemed judicious, therefore, to pursue further the work of Ambache and examine the autonomic-like effects of (1) not only whole iris tissue but, also of (2) the iris dilator pupillae, of, (3) the iris sphincter pupillae, of (4) ciliary muscle tissue, and of (5) ciliary process tissue. Observations of interesting autonomic-like effects of these various tissue extracts resulted.

METHODS

1. *All assay procedures* were performed on rat colon in a 37.5°C., 35 ml. muscle bath, and in the presence of oxygenated de Jalon solution. All extracts were prepared from hog eyes.

2. *Dissection of the tissues.* The eyes were prepared for dissection as previously described.[4] Sphincter pupillae and dilator pupillae were dissected from (the same) eyes at one time, and ciliary muscle, ciliary process, and whole iris tissue were dissected from (the same) eyes at other times. The dissections were arranged in this manner because of the necessarily laborious and time consuming procedures involved. It was, of course, desirable not to prolong the dissection for obvious reasons of tissue decomposition. It should be made clear that the sphincter pupillae dissection involved the removal of an approximately 1.0 to 1.5-mm. strip of sphincter tissue around the central (pupillary) edges of the iris. When this was removed, the remainder of the iris was teased away, so that what we refer to as dilator pupillae is really dilator pupillae plus remnants of sphincter pupillae. The ciliary process dissection was according to the methods previously described.[4] After these ciliary processes were removed, the attached remnants were cleared away as cleanly as possible. The whole iris was then teased away with forceps. Following this, the ciliary muscle was, also, teased away with forceps. It should again be made clear that what is referred to as ciliary muscle consisted of remnants of unremoved ciliary process and of remnants of unremoved iris, as well as ciliary muscle.

3. *Preparation of extract.* A modification of the procedure used by Ambache[2] was employed for our tissue extractions. After tissue was dissected, it was usually frozen until needed. Freezing of the fresh tissue did not seem to alter the potency of the extracts tested. The thawed or fresh tissue was cut into small bits with a fine scissors. This preparation was done in a 3°C. cold room. The macerated tissue was then transferred to a Teflon pestle glass homogenizer which was in turn placed in a jar loaded with cracked ice. The tissue was then homogenized (100

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mg./ml. in the presence of a neutral aqueous solution, adjusted to pH 7.0 with weak sodium bicarbonate solution) to a very fine suspension by attaching the steel shaft of the pestle to a medium-speed power drill-press. The preparation was then transferred to a lusteroid centrifuge tube and spun for ten minutes at 2,000 rpm. It should be clarified that if the muscle tissues were not first macerated with scissors, then complete grinding with the Teflon pestle was not possible. The ciliary process tissue did not require this maceration treatment prior to the homogenization. The supernatant was decanted-off and frozen at −30°C. for one to three days and then thawed, at which time the centrifugation procedure was repeated. The supernatant from the latter procedure was adjusted to pH 2.2 with weak hydrochloric acid solution. To this was added an equal volume of ether. Following vigorous mixing, the ether fraction, which now contains the active extract desired, was removed and transferred to a glass container. The ether was driven off by a current of air and the residue which was left behind was then mixed with de Jalon solution so as to restore the original volume of the homogenized whole tissue suspension.

TABLE 1

HOG CILIARY PROCESS AND HOG IRIS EXTRACT EFFECTS ON RAT COLON

Experiment	Order of Addition of Drug or Tissue Extract	Tissue Wet Weight Equivalent in Final Extract (mg.) (repeated additions)	Cumulative % Increase over Pretreatment Tone
12	Process	563	18
	Atropine 5×10^{-7} M	—	0
18	Process	300	7
	Process	200	10
	Atropine 5×10^{-7} M	—	5
13	Process	428	9
13	Process	564	4
16	Process	400	8
	Whole iris	130	22*
18	Whole iris	300	24
	Whole iris	200	26
	Atropine (10^{-6} M)	—	22
12	Whole iris	634	35
	Atropine (10^{-6} M)	—	38
13	Iris	606	3
	Iris	503	16
	Atropine 5×10^{-7} M	—	11
16	Iris	500	7
	Atropine 5×10^{-7} M	—	10
	Process	500	12*

* High amplitudes of contraction.

Horizontal lines indicate use of a new muscle or a washed muscle. Muscle bath and all solutions made with de Jalon's solution. O_2 bubbled in bath.

RESULTS

1. *The effects of ciliary process and iris extracts* are illustrated in Table 1. While ciliary process extracts clearly increased muscle tone, these effects are reversed by atropine. Iris effects are generally unchanged in the presence of atropine. Ciliary process and whole iris in the same system seemed to behave in a more than additive fashion. If atropine is added this effect is markedly reduced. The atropine effects on ciliary process and iris extracts are illustrated in Figure 1.

2. *Sphincter and dilator pupillae and ciliary muscle effects* are shown in Table 2.

a. Sphincter pupillae extract seems to have little effect on muscle tone, but it does, after a short latency period, seem to induce greater frequency of contractions. Results similar to this have been observed in other systems having three times the amount of sphincter pupillae extract. Sharp rises in contraction were observed, however, when doses markedly exceeded this level.

b. The results indicate, too, that when sphincter pupillae extracts are added to dilator pupillae extracts a marked response occurs.

c. The dilator pupillae effects are clearly different, and greater than, the sphincter pupillae effects. These sphincter and dilator pupillae effects are illustrated in Figure 2.

3. *Ciliary muscle extracts* clearly induce marked increases in muscle tone (table 2).

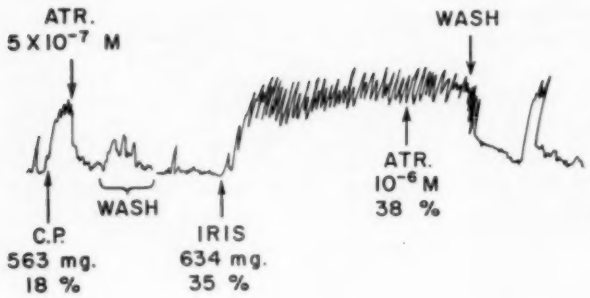

Fig. 1 (Waitzman). Atropine effects on hog ciliary process and hog iris extracts. (CP) ciliary process, (ATR) atropine, (%) figures indicate the maximum percent increase of a given treatment over pretreatment tone.

Fig. 2 (Waitzman). Smooth muscle-stimulating action of sphincter and dilator pupillae extracts. (%) figures indicate the maximum percent increase of a given treatment over pretreatment tone.

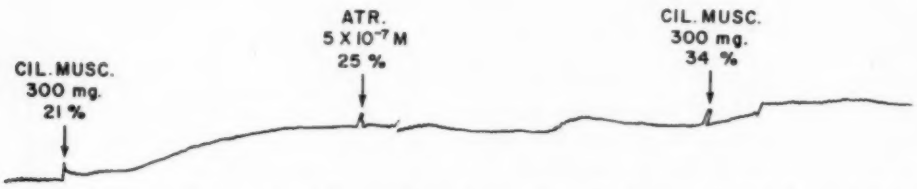

Fig. 3 (Waitzman). Nonreversing influence of atropine on ciliary muscle extracts. (%) figures indicate the maximum percent increase of a given treatment over pretreatment tone.

This ciliary muscle effect is not reversed by atropine nor, when this effect reached an apparent peak with several additions of ciliary muscle extract, is the effect further modified by either iris or ciliary process preparations. The nonreversing influence of atropine on ciliary muscle extract is shown in Figure 3. The fact that atropine does not reverse the effect of ciliary muscle extract but does reverse the effect of acetylcholine added to the same system is shown in Figure 4. It seems, in fact, that atropine has a slight enhancing effect on ciliary muscle extract systems.

In experiments with extracts that had been made to the final stage with de Jalon solution and then frozen for 24 hours and thawed just prior to assay, activity seemed unaffected. The assays being reported here were, however, always done with fresh preparation immediately following the ether extraction phase.

Rabbit aqueous humor which was acidified, extracted with an equal volume of ether, and the ether residue taken up with a similar volume of de Jalon solution, showed no smooth muscle activity effects.

Discussion

The results with repeated experiments were at times variable, but this has not affected the nature of the findings. Future studies will include attempts to seek the causes of these variations.

One can only speculate as to the significance of the above findings. It is clear that extracts of the whole iris do not behave the same as extracts from its two major components. It is of great interest that the sympa-

Fig. 4 (Waitzman). Combined atropine-acetylcholine effects on ciliary muscle extract system. (%) figures indicate the maximum percent increase of a given treatment over pretreatment tone. (ACh) the percent of acetylcholine added.

thetically innervated dilator pupillae produces substances which have a profound effect on the parasympathetically activated rat colon muscle, and that the parasympathetically innervated sphincter pupillae has much less an effect on this same muscle preparation. It is possible to conceive of a sympathomimetic substance in the iris being released by the parasympathomimetic substance (or substances) of the iris, the former substance in turn acting on the regulation of blood vessel patency, or acting in some other manner. Pressor-effect assays on iris extracts are contemplated.

TABLE 2

RAT COLON-STIMULATING EFFECT OF COMBINED OCULAR EXTRACTS

Experiment	Order of Addition of Drug or Tissue Extract	Tissue Wet Weight Equivalent in Final Extract (mg.) (repeated additions)	Cumulative % Increase over Pretreatment Tone
15	Sphincter pupillae	43	1*
	Dilator pupillae	200	26
15	Dilator pupillae	200	12
18	Ciliary muscle (c.m.)	500	52
	Atropine 5×10^{-7} M	—	48
16	Ciliary muscle	300	21
	Atropine 5×10^{-7} M	—	25
	Ciliary muscle	300	34
	Ciliary muscle	500	42
	Atropine (10^{-6} M)	—	45
	Whole iris	200	45
	Process	200	45
18	Process	280	5
	Ciliary muscle	200	16
	Ciliary muscle	200	21
16	Ciliary muscle	400	16†
	0.00014% Ach	—	62
	Atropine 5×10^{-7} M	—	19

* Greater frequency of contraction after latency of about 20 seconds.

† Marked reduction of contraction amplitudes.

Horizontal lines indicate use of a new muscle or a washed muscle. Muscle bath and all solutions made with de Jalon solution. O_2 bubbled in bath.

Concerning the ciliary muscle extracts—one cannot be sure of the physiologic role of this preparation, but, undoubtedly, it plays a role related to one or more functions. These could be some humoral effect related to the accommodation reflex, to regulation of vascular patency or, perhaps, to regulation of patency of drainage channels for aqueous humor. As was stated, Ambache[3] did report an irinlike substance in aqueous humor in eyes which had been subjected to paracentesis. Whether such a substance was going to or coming from its site of action is not clear, but we contemplate studies to clarify this point. We were, however, not able to detect activity in aqueous from postmortem rabbit eyes.

The acetylcholinelike nature of extracts from ciliary process might be of special interest. This was the only extract tested, the effect of which was reversed by atropine. The significance of this in relation to aqueous production will be studied further.

SUMMARY

1. Parasympathomimeticlike effects, not acetylcholinelike in nature, are described for extracts of dilator pupillae, ciliary muscle, and iris tissues from hog eyes.

2. Parasympathomimetic effects which are acetylcholinelike are demonstrated for extracts of hog eye ciliary processes.

3. The possible significance of the above findings are discussed.

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CLINICAL EXPERIENCES WITH THE PHOTOCOAGULATOR*

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Little has appeared in the American literature concerning Meyer-Schwickerath's photocoagulator. This is surprising, since the instrument represents a remarkable advance in ocular treatment. Basically, the photocoagulator (fig. 1) is an intense source of light from the visible portion of the spectrum, precisely focused, and ingeniously controlled so that therapy can be carried out under constant ophthalmoscopic observation. The desired therapeutic effect results when this intense light is absorbed by a pigmented structure, and is thereby transformed into heat. The result varies from a slight chorioretinal inflammation and subsequent adhesions, to the explosive vaporization which can blast a new pupil through the center of an updrawn iris. Variable voltage, an adjustable diaphragm, a series of apertures of different sizes, and control of the time of exposure permit the operator to achieve any desired intensity of treatment.

The two most effective uses of photocoagulation are the creation of chorioretinal adhesions in an area where the retina and choroid are already in contact with each other, and the formation of a new pupil in the center of an updrawn iris. In addition, some types of unwanted tissue can be destroyed (neoplasm, inflammation).

Chorioretinal adhesions cannot be achieved unless these two tissues are touching each other, any more than two sheets of metal can be welded together if they are not in contact. This means that a detached portion of retina cannot be effectively reattached with photocoagulation.

The ideal case for photocoagulation is that of a patient who has just developed a symptomatic retinal hole which has not yet produced a detachment (fig. 2). Such a patient consults his physician because of the typical premonitory symptom of sudden onset of floating opacities. These opacities are usually due to slight vitreous hemorrhage, the extent of which is determined by the size of the blood vessels disrupted by the retinal break. Floaters may also represent pigmentary or cellular debris, an operculum, or con-

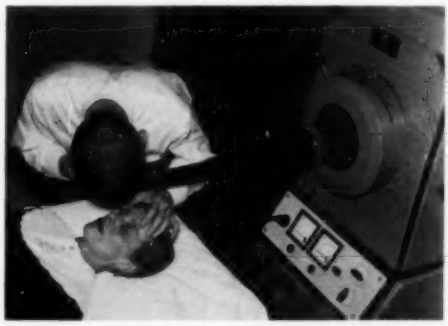

Fig. 1 (Havener). The photocoagulator.

* From the Department of Ophthalmology, Ohio State University.

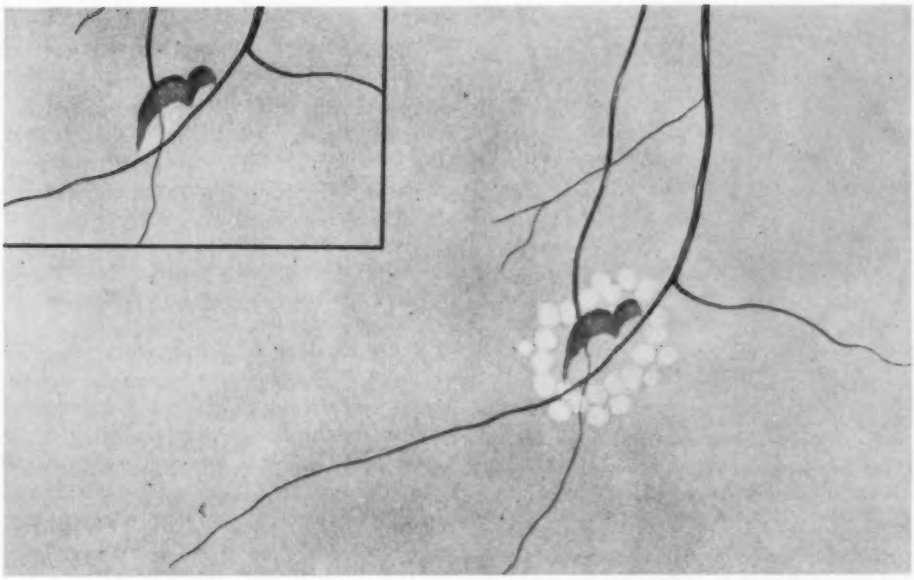

Fig. 2 (Havener). Inset: a peripheral retinal tear with minimal surrounding detachment, as observed 3 days following onset of a small vitreous hemorrhage. Main picture: same lesion after sealing by photocoagulation.

densations in the vitreous. Development of a retinal hole can be differentiated from the symptomatically similar, and far more common, posterior detachment of the vitreous only by very careful ophthalmoscopy (preferably indirect) through a well-dilated pupil. Both of these entities may produce Foster Moore's subjective lighting streaks. Vitreous hemorrhage of sufficient magnitude to be observed with the slitlamp commonly results from a retinal tear, and only very rarely from posterior vitreous detachment unassociated with a retinal tear.

While it is recognized that asymptomatic holes may be found during routine clinical examination and in study of autopsy eyes, and that occasional symptomatic holes are followed for a long period of time without development of detachment, nevertheless it is definitely desirable to seal symptomatic holes with photocoagulation. This conclusion is inescapable when the almost insignificant risk of photocoagulation is balanced against the high incidence of detachment following such retinal tears, and the relatively poor prognosis of detachment surgery in even the most expert hands. Because of macular involvement, subsequent development of additional holes, surgical failure, and other complicating factors, more than a third of eyes suffering detachment are not restored to reading vision. Significant statistics concerning the incidence of detachment from untreated symptomatic holes are almost impossible to obtain. Reasoning backward from detachment patients does not provide such statistics but certainly indicates the great frequency with which symptoms characteristic of retinal hole formation precede actual detachment.

Prophylactic photocoagulation of suspicious pigmented or latticelike areas in the absence of holes is not indicated unless detachment has already occurred in the same or fellow eye on the basis of a similar lesion. A variety of lesions (for example, focal chorio-retinal atrophy) may somewhat simulate a retinal hole. Use of indirect ophthal-

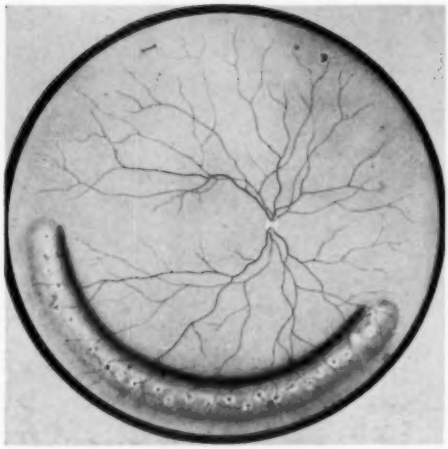

Fig. 3 (Havener). This patient with degenerative myopia and an inferior detachment had four holes in the detachment and three superiorly in the flat retina. Scleral infolding below was supplemented by photocoagulation of the three upper holes, thereby reducing the amount of surgery necessary.

moscopy with scleral depression and the three-mirror Goldmann retinal prism are the two most accurate methods of differentiating a true retinal hole from simulating lesions. Macular holes are usually not through-and-through lesions and, therefore, the majority should not be coagulated.

Another important use for photocoagulation is as a supplement to standard surgical procedures for retinal detachment. Figure 3 illustrates such a case in which seven holes were present. The four inferior holes were in a detached area and were sealed by a standard scleral infolding surgical procedure. Photocoagulation sealed the upper three holes, which were within a still-attached retinal area, without the necessity of surgical trauma in the upper portion of the eye. Such supplementary photocoagulation can be applied before or after surgery. Not infrequently during the postoperative period, the surgeon wishes he had applied a little more diathermy in a critical area. With the photocoagulator, precise placement of this additional treatment is possible, and may make the difference between success and failure. Sometimes an isolated peripheral area will develop a recurrent detachment after several temporarily successful operations. If this recurrent detachment is partially walled off and relatively small, photocoagulation may be used to create a barrier which will prevent further extension. The walled-off detachment then remains harmless and stationary in the periphery.

A relatively uncommon use for the photocoagulator is the sealing of holes in detachments which have settled completely with bed rest. At least 90 percent of detachments will not settle adequately for such treatment, but it may be well to try a reasonable period of bed rest with binocular patching, especially if the hole is in a relatively inaccessible position, such as far posterior or in an extensively scarred region (fig. 4). Presence of visible vitreous traction bands almost excludes the possibility of such settling.

The technical details of photocoagulation for the purpose of creating chorioretinal adhesions deserve comment. Maximum dilatation of the pupil (one-percent Cyclogyl and 10-percent Neosynephrine) is most impor-

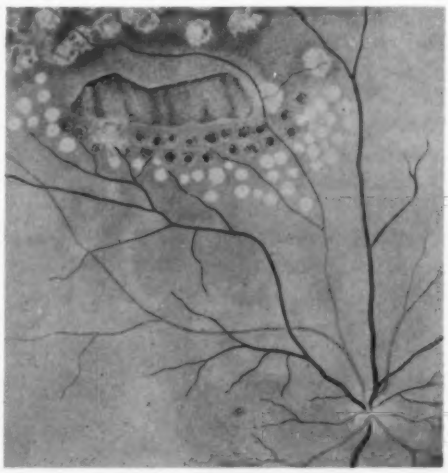

Fig. 4 (Havener). A very large hole posterior to the equator and behind the diathermy scars of five temporarily successful previous operations. Bedrest permitted settling of this detachment and photocoagulation successfully sealed the hole.

tant, since the entrance aperture determines the amount of light which is available for therapeutic effect. The area of the pupil opening increases proportionately to the square of its radius. A large pupil is particularly vital if the region to be treated is peripheral, since the effective entrance area of the pupil decreases rapidly as the angle of illumination becomes more oblique. If the media are clear and the pupil can be widely dilated, photocoagulation can be achieved almost as far peripherally as can be seen with a direct ophthalmoscope. Corneal scars, cataract, or vitreous opacities disperse the light, and if sufficiently dense will preclude use of photocoagulation. In general, if the lesion can be seen recognizably well with the direct ophthalmoscope, opacities of the media are not dense enough to block photocoagulation. In two patients I have effectively sealed retinal tears through diffuse vitreous hemorrhage so dense that direct ophthalmoscopy could only localize the lesion but not identify its nature (diagnosis made by indirect ophthalmoscopy).

Retrobulbar injection of five cc. of one-percent Xylocaine is usually helpful. The sensory block of the optic nerve so obtained eliminates patient discomfort and resultant blinking or eye movement due to the intense light. The proptosis obtained by this volume of retrobulbar compensates for inability of the patient to rotate his eye, though this may easily be done with a muscle hook if necessary in treatment of the far periphery. Chorioretinal photocoagulation is not particularly painful, and can be done in cooperative patients with reduced vision without any anesthesia whatsoever. Slight movements of the eye are very annoying, since they interfere with localization of the area to be treated. Worst of all, if the minimum intensity technique shortly to be described is used, between a half to one second exposure time is necessary, and no coagulation results if the retina shifts during this time.

The cornea is quite susceptible to drying during photocoagulation. Constant attention must be paid to keeping it moist, whether by irrigation or closing the lids between each exposure. If corneal haziness is permitted to develop, it interferes seriously with localization, and produces sufficient light scatter to block the coagulation effect. Sometimes a five minute rest period will result in enough clearing that therapy can continue. If not, treatment must be postponed until later. Within a day, this corneal haze is always gone, and has not been observed to leave any permanent opacity. An assistant is often very helpful in holding the lids apart and moistening the cornea.

Localization of the area to be treated is of paramount importance. Because the photocoagulator ophthalmoscope is clumsy and difficult to maneuver, detailed preliminary examination is necessary. Conspicuous details such as vessel bifurcations, hemorrhages, pigment, and so forth should be sought out and will serve as identifying marks. At intervals during a session of photocoagulation, examination with the indirect ophthalmoscope provides a clear and wide field of view which permits rapid determination of how much remains to be done.

Positioning of the patient is simplified by use of a standard four-wheeled stretcher cart such as is commonly used in hospitals. This permits the patient to be moved about easily in relationship to the photocoagulator. A doubled pillow beneath the patient's head provides the proper height. His chin should be tilted up quite high to prevent his forehead from interfering with the free movement of the instrument arm, otherwise the treating ophthalmoscope cannot be brought optimally close to the eye. Head turning may sometimes be necessary to accomplish the same purpose. Coagulation is much easier straight down or when the light beam is angled back toward the body of the photocoagulator. I find manipulation of the instrument very unsatisfactory when the beam is angled very far away from the photocoagulator, and prefer to rotate the patient

180 degrees to avoid such positions. The problem with these "away" positions is that the operator must view the field obliquely through the pinhole and he does not have a large enough viewing aperture for easy use.

The tendency for the instrument to move slightly when the push-button is activated may be eliminated by a firm grip with all the hand except by the thumb or finger preferred by the operator. Steadying the instrument arm with the other hand is helpful. Diffusion of light to adjacent portions of the retina may permit as much as a millimeter error in positioning of the treated area. The operator must position the bright central portion of the light on the area to be coagulated, and should not be misled by the peripheral diffusion of light. Such an error is possible because the illuminated area is greater than the visible area, and the operator may not realize he is viewing the periphery of the illuminated area. Recognition of the possibility of this error permits its avoidance.

Choice of apertures and intensity of light is fairly simple. In general, the largest treatment diameter should be used. This will be reduced in size if the pupil does not dilate well, in order to avoid heating the iris with the edges of the beam. Iritis may result if a misdirected beam or an excessively large one overheats the iris too severely. A smaller aperture is also used to treat a tiny lesion near the macula or disc. More intense light is required to obtain the desired effect with smaller apertures.

It is wise to start with the lowest voltage setting and a partially closed diaphragm in order to eliminate any possibility of causing an excessive reaction. Actually, most human eyes diseased enough to demand coagulation will require more than the minimum setting. Successive exposures are then made, as the diaphragm is opened to its maximum and the voltage increased stepwise until the desired effect is attained. With experience, these steps require very little time.

The optimal strength of light is that which produces a visible effect developing slowly within a half to one second. The operator is alert to release the button as soon as the whitish response of tissue coagulation is perceived. Less intense light will not produce an adequate response because the cooling effect of the circulating blood prevents accumulation of enough heat. More intense light risks the danger of excessive destruction before the reflex time of the operator can turn off the current. Too intense a burn may produce a retinal hole or induce vitreous shrinkage, and must be carefully avoided. Actually, considerable leeway is present in this procedure and it quite easy to avoid overtreatment.

Variations in pigmentation make an appreciable difference in the amount of light required. Pale areas absorb less radiation and may be quite difficult to treat. Retreatment of the same spot requires more intensity because of the color change. Definite haziness of the posterior vitreous adjacent to the treated spot occurs, and requires an increase in light as treatment progresses. Since peripheral areas require more intensity and are harder to focus upon, it is wise to begin on the most peripheral portion of the lesion and work posteriorly.

A solid barrier of coalescent burns should be laid down around the retinal edge of an undetached hole. This barrier should be about a millimeter wide. No advantage accrues from more extensive burns. When walling off a peripheral detachment, however, two or three rows of coagulation are required for security. Vessels in the region which must be coagulated are a nuisance. A "hot shot" on a vessel can cause immediate explosive hemorrhage, or delayed bleeding when the burned wall becomes necrotic. Fortunately, the "minimum intensity technique" just described does not seem to damage vessels. The operator should be exceedingly careful, however, to attain only the slightest grey discoloration on those burns which overlie a vessel. If desired, the vessel may be paralleled by coagulation a little way beyond the lesion.

Although one might expect fibrin clots to strengthen the chorioretinal attachment almost immediately, animal experiments do not seem to bear this out. Even after several days, only the slightest degree of chorioretinal adhesion is demonstrable. Even a single "hot shot" will weaken the retina enough so that manipulation of the experimental eye causes a retinal hole. Furthermore, exudation from a burned choroid may produce a local retinal elevation just as placing your finger on a hot stove causes a blister beneath the skin. Because of these factors, the retina is almost certainly weaker immediately after coagulation than it was before. I am reasonably certain that several days of binocular patching and limited activity should be advised following most cases of photocoagulation, and that under these circumstances the "minimum intensity technique" is quite safe.

Formation of a new pupil (fig. 5) is an entirely different use of the photocoagulator and even requires different attachments. A converging beam of light is used, and focuses sharply upon the iris through a water bath. This precorneal pool of water is held by placing a plastic cylinder firmly against the sclera. Without the protection of this water, severe corneal burns may result. Despite use of water, corneal burns occur if the anterior chamber is so shallow that the cornea is within a millimeter of the iris. Similarly, if the lens is present, a localized cataract will form beneath the heated areas of iris. The ideal case for this use of the photocoagulator is the deep-chambered aphakic eye with an updrawn pupil or a pigmented secondary membrane. Nonpigmented cortical masses, clear capsule, or gray vitreous opacities cannot be removed by photocoagulation.

In contrast to the "minimal intensity technique" for producing chorioretinal adhesions, the highest intensity of the machine is used for creating new pupils. The focusing light is precisely adjusted in accurate focus on the iris in the center of the eye, and a half-second to one-second flash of light delivered. The desired end-point is an explosive "pop," clearly audible to everyone in the room, and visible as a bubble of steam which appears suddenly at the point of focus, literally blasting apart the iris. This cannot always be attained, and if it does not occur, coagulation beyond one second is very hazardous to the cornea. Three separate corneal portals of entry may be used if necessary one central, one above, and one below. In this way three separate flashes of light may be applied to the same portion of iris without risking the corneal scarring which may result from excessive light. Should this not

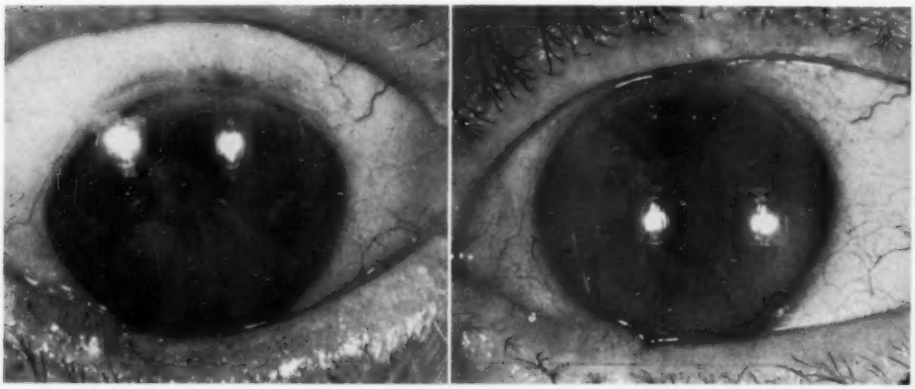

Fig. 5 (Havener). Before and after photocoagulation of a new pupil through an updrawn iris following cataract extraction.

produce an adequate pupil, it is best to postpone further attempts. Often the burn, though insufficient to explode a pupil, will cause enough damage so the treated portion of iris will atrophy away during the next few weeks. Mydriatics will help to form or maintain the new pupil.

Destruction of unwanted tissue in the posterior portion of the eye calls for varying intensities of treatment. In general, retinoblastomas, angiomas, and melanomas may respond to photocoagulation. In order to treat a malignant tumor, its entire circumference must be visible. While a small growth may actually be burned up through repeated coagulations, a more effective mechanism of destruction is the coagulation of the tumor blood supply. This is achieved by encircling a peripheral neoplasm with a solid ring of heavy photocoagulation which cuts off both retinal and choroidal vascularization of the encircled area. Obviously this is not effective against growths in the posterior pole where short posterior ciliary arteries enter directly. Large vessels leading to a tumor should not be hit with such heavy coagulation, or severe hemorrhage develops. The large feeder vessels of a retinal angioma are said to shrink following treatment of the angioma itself. In addition to encircling tumors, the photocoagulator beam should be directed against the substance of the lesion, with a high intensity light. The surface layers can be destroyed in this fashion, but deeper tissue is not killed by one treatment.

Experience in tumor therapy with the photocoagulator is insufficient to permit specific recommendations at this time. However, a trial of photocoagulation of small and accessible chorioretinal tumors seems reasonable and is advised. Rather dramatic cases of several years of "cure" of retinoblastoma and melanoma exist.

Treatment of focal chorioretinitis and perivasculitis is in the experimental stage. It is possible that the course of such inflammations may be appreciably shortened by photocoagulation.

Summary

The clinical indications for photocoagulation are:

1. Creation of chorioretinal adhesions: (a) sealing of retinal holes before detachment; (b) supplement to surgery—combined photocoagulation and surgery, reinforcement of diathermy reaction, and walling off limited detachments; (c) sealing of holes in the uncommon detachments which settle completely with bedrest.

2. Formation of new pupil: (a) updrawn pupil and (b) pigmented secondary membranes.

3. Destruction of unwanted tissue: (a) neoplasm and (b) inflammation.

Photocoagulator use and the "minimum intensity technique" are described.

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AN HYPOTHESIS CONCERNING THE ETIOLOGY OF NONPARALYTIC STRABISMUS*

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In summarizing the evidence regarding the etiology of comitant strabismus, Adler states, "a large number of patients with strabismus can be proved to have neither a sensory or motor obstacle to fusion . . . this group of patients are sometimes said to have

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strabismus on the basis of undetermined etiology."[1] The purpose of the present paper is to state an hypothesis concerning the etiology of strabismus in patients of this type.

According to Gesell[2] and Piaget,[3] it is not until the age of about four months that human infants start to learn that their visual images represent things which can be touched and manipulated. Consider an infant, who at this age, has a temporary or remediable obstacle to fusion, such as delayed myelinization of the oculomotor fibers. Then, during this period of sensory-motor development, the infant will see two different images of every object, and the two will appear to be in different places. If the child's perceptual development is to continue, one of the images must be chosen as representing the object. The remaining image will then be perceived as unreal, in the sense that it will appear to be devoid of tactile-kinesthetic properties. It will look like a mere image, a thing that cannot be touched. There is no difficulty in assuming that the child can learn to do this, for during this stage of growth he learns that there are many visual stimuli which can be seen but not touched: mirror images, cigarette smoke, sunbeams, and so forth.

As an aid in differentiating between real objects and their unreal images, the strabismic child adopts the technique of perceiving all images associated with one eye as real, and all images associated with the other eye as unreal. It is this perceptual pattern which underlies the distinction between fixating eye and nonfixating eye in strabismus.

Let us assume that the original obstacle to fusion persists only until the child is one year old. My hypothesis is that the real-unreal distinction, between images associated with the fixating eye and images associated with the nonfixating eye, now constitutes an obstacle to fusion and accounts for the persistence of the strabismic condition in the absence of any physiologic causative factor.

The ages and time intervals specified in the foregoing accounts are purely illustrative. The same sequence of events—temporary obstacle to fusion, perceptual adaptation, disappearance of the original defect, and persistence of the strabismic condition—may occur even in an adult patient. The process may require several years in an adult who has an injured external rectus; whereas the same process—learning to interpret one image as unreal—may require only a few hours during the period of infancy when sensory-motor maturation is the chief business of living.

This real-unreal distinction can be observed in any patient with a well-established strabismic condition who is aware of diplopia for an object. It has escaped observation by previous investigators because of the widespread practice of examining patients on a troposcope or similar instrument, particularly for research purposes. On the troposcope, all images are unreal; but if a strabismus patient can be made aware of diplopia for a real object, he will readily agree that the image associated with the fixating eye is "the real one," whereas the image associated with the non-fixating eye is "unreal" or "fake" or "make believe." In carrying out this examination, no prism should be placed before either eye. The reason for this is that the distortion in apparent position caused by the prism may be sufficient to cause one of the two images to appear unreal, thus invalidating the observation.

A normal binocular individual who is aware of diplopia for an object may also perceive one image as real and the other image as unreal. But he does not make this distinction as easily or as accurately as the strabismus patient does. The true strabismus patient does not have to make a conscious judgment in choosing between the two images. As soon as he sees them, he involuntarily sees one as real and the other as unreal, as if these properties of reality and unreality resided in the stimuli themselves.

To understand why the real-unreal distinction is an obstacle to fusion, consider the mechanism of normal binocular fusion. When a normal individual fuses two images,

he does so because he interprets both of them as representing the same object. We would hardly credit him with normal binocular vision if he were to fuse the images of two different objects in the field of view. The two images having been interpreted as representing the same object, the appropriate optomotor reflexes are called upon to position the eyes in such a way as to combine the two images, and the two are seen as one. In strabismus, on the other hand, the two images of a single object are not interpreted as representing the same thing. One represents a real, solid object, whereas the other represents nothing, only itself—a mere image. As a result, the optomotor reflexes appropriate to bifoveal fixation are not called into play, and an abnormal pattern of binocular vision results.

The real-unreal distinction also constitutes the mechanism of suppression in strabismus. A simple analogy will serve to illustrate this part of the hypothesis. Consider a patient who has a disturbance of the ocular media which causes him to see a stone wall directly in front of him at all times. The patient can see other things through the stone wall and even in the same place as the stone wall. He cannot touch or approach the stone wall, because this is a strictly ocular disorder. Given an early onset of this condition, the patient will gradually become unaware of the stone wall. He will not see it except under special conditions of viewing or with the aid of a course of training in stone wall awareness.

A less hypothetic analogy is to be found in the entoptic images associated with cellular debris and other opacities in the refractive media of the human eye. One can easily learn to be aware of these phenomena under ordinary conditions of viewing, and they are evidently present as visual stimuli at all times. When seen, they are perceived as unreal, and the observer makes no effort to approach or touch them. The analogy is quite direct: the strabismus patient is not ordinarily aware of his squinting eye images for the same reason that I am not ordinarily aware of my muscae volitantes and other entoptic images.

Experimental evidence supporting this entire retionale for the etiology of strabismus has been presented in a different context in two previous papers. The evidence is of course indirect, for it is not feasible to evaluate the subjective visual experience of three-month-old infants. In the first paper of the series,[4] it was shown that lessening of the real-unreal distinction has the effect of reducing the intensity of monocular suppression in strabismus patients, so that the patients tend to become acutely aware of diplopia. The presence of constant diplopia has not been a source of confusion or annoyance to any patient who has participated in this program of research.

The second paper of this series[5] presented evidence that the real-unreal distinction constitutes an obstacle to fusion. In this experiment, it was shown that lessening of the real-unreal distinction, in patients who were already aware of diplopia, made some of the patients capable of fusion. The patients who responded to this treatment actually overcame angles of strabismus of as much as 30 prism diopters, indicating the presence of intact optomotor reflexes which had not been brought into play simply because of the interpretation of images associated with the nonfixating eye as unreal. This method of treatment is by no means a cure-all for comitant strabismus, but the results so far obtained are sufficient to indicate that the real-unreal distinction, as it exists in strabismus, is a major obstacle to fusion and a prominent etiologic feature of the disorder.

If the hypothesis set forth here is a correct statement of the etiology of strabismus, then the following inferences from it are also correct:

First, the condition described by Adler as strabismus of undetermined etiology is an acquired disorder. Therefore it is, in principle, remediable.

Second, the genetic facts are to be accounted for in terms of the temporary physiologic or anatomic cause of onset, and not in terms of any undetected physiologic condition assumed to be present at the time of examination.

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HOW VALID IS A SCLERAL TONOMETER?*

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The diagnosis of glaucoma is at best a most difficult task, tonometry being one of the many adjuncts in the detection of this disease. Any clinical tonometer, regardless of how accurate, must be considered in the light of what it really contributes to the diagnosis and management of glaucoma. The scleral tonometer which was introduced over 10 years ago[1] has enjoyed a certain amount of popularity. Its working principles are similar to those of the well known corneal (Schiøtz) tonometer but it does not require conjunctival anesthesia and it can be used with the patients in a semi-reclining position.[2,3]

Although the scleral tonometer has been used within the past decade studies of its validity are incomplete. Hirsch[4] found that the correlation coefficient between the second and third repetitions of measurements with the scleral tonometer was +0.77 and this gives an indication of how reliable the instrument is. Talcott[3] made measurements with both the corneal and scleral tonometer on 23 patients and found a correlation coefficient of +0.85 and concluded that this validated the instrument. On the other hand Cockburn[5] made a study of the scleral as compared to the Schiøtz tonometer on 22 eyes known to have glaucoma and 22 non-glaucomatous controls. The corneal tonometer quite accurately differentiated these two groups (with only two false positives and one failure) while the scleral tonometer failed to differentiate the two groups and allowed only poor discrimination.

Carter[6] also has made a study of the scleral tonometer with regard to theoretical considerations relating to its use but his measurements do not include any thorough analysis of the validity of the instrument.

The present study was undertaken to determine how accurately the scleral tonometer measures the intraocular pressure with respect to the standard corneal instrument which has been in use for over 50 years.

Procedure

Two separate experiments were carried out:

1. Freshly enucleated adult pig eyes were used in the following manner: Each eye was cannulated through the optic nerve[6] where-

* From the Department of Ophthalmology, University of Michigan. Presented at the meeting of the East-Central Section. Ann Arbor, January, 1960.

upon alternate aspirations and injections of saline were carried out to insure patency of the needle. The eye was then placed in a slotted lacrimal irrigation cup and its surroundings packed with excised retrobulbar fat and muscles. The rim of the cup was encircled with nondrying putty to prevent the semifluid fat from shifting during the experiment. The cannula was connected, through polyethylene tubing, to an open tube water manometer. A three-way stopcock was interposed into the system to make possible the controlled variations in intraocular pressure by means of a reservoir which could be raised and lowered.

Each eye was subjected to intraocular pressures of from 25 to 100 cm. of water at increments of five cm. At each pressure level the ocular tension was estimated by first closing the stopcock completely, moistening the eye, applying the Schiøtz and then the Wolfe tonometer according to prescribed procedure. Early in the course of gathering these data, three separate readings were made with the Wolfe instrument (accepted technique),[3] the first being discarded, and the second and third were averaged to achieve the final recording.† This procedure was abandoned when it was noted that a single reading gave essentially the same result. The Schiøtz recordings were made employing weights which would allow for scale readings of between three and ten and were transposed to the 1955 calibration scale of the American Academy of Ophthalmology and Otolaryngology.

2. Using the Wolfe and Schiøtz instruments, estimates of intraocular pressures in 44 clinic patients (86 eyes) were carried out. In each instance Pontocaine HCl (0.5 percent) was instilled and the Schiøtz measurements were made according to the standard procedure. The patient was then brought to a semireclining posture and asked to fixate his opposite hand while the Wolfe tonometer, used horizontally, was applied to the upper outer quadrant in such a manner that its footplate was four or more mm. from the limbus and between the insertions of the lateral and superior rectus muscles.

† Hirsch found the test-retest coefficient between the first and second tests to be +0.56; between the first and third tests to be +0.49, and between the second and third test to be +0.77.

Results

The results of the above experiment on the 11 pig eyes are summarized in Fig. 1. This figure shows the mean measured pressure with each instrument for various controlled pressures. The slope of the straight lines which are drawn through the data can be regarded as indices of the sensitivity of the instruments. The data for the corneal tonometer approached perfect sensitivity reasonably well. The slope of the best fitting straight line is +0.910. This means that on the average, change in the induced intraocular pressure of 10 mm. Hg will be detected by this tonometer as a 9.10 mm. Hg change in intraocular pressure. On the other hand

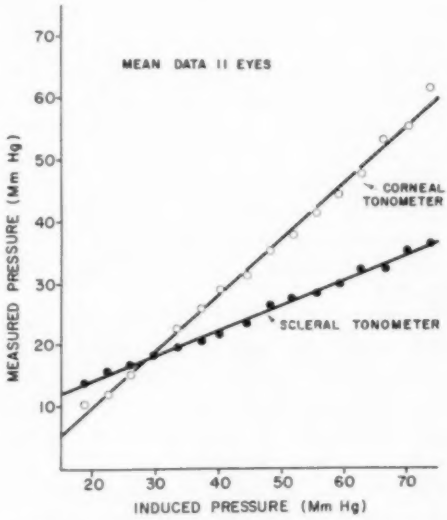

Fig. 1 (Hogg and Alpern). Mean data of the manometric measurements of 11 pig eyes with the corneal (open circles) and scleral (closed circles) tonometers. The straight lines have been computed by the method of least squares. The slope of the corneal line is 0.91, that of the scleral line is 0.392.

TABLE 1

ANALYSIS OF VARIANCE MEAN DATA 11 EYES

	A. WOLFE			
	S.S.	D.F.	M.S.	F.
Slope	19,844.16	1	19,844.16	238.86
Scatter	686.08	14	41.86	0.501
Deviations	13,293.08	160	83.08	
Total	33,823.32	175	193.27	
	B. SCHIØTZ			
	S.S.	D.F.	M.S.	F
Slope	41,833.18	1	41,833.18	518.64
Scatter	214.11	14	19.46	0.2412
Deviations	12,905.95	160	80.66	
Total	54,953.24	175	314.02	

the scleral tonometer proved to be considerably less sensitive. In this case the slope of the straight line which best fits the data is merely 0.392. Hence, on the average, a change of induced pressure of 10 mm. Hg within the eye would only be detected by the scleral tonometer as a 3.92 mm. Hg rise in pressure.

In order to investigate this matter further, all of the data for a given instrument, from the 11 pig eyes at the 16 different levels of induced pressure were pooled and an analysis of variance carried out. The results of this are summarized in Table 1. While in each case the slope is clearly significantly different from zero, the variance due to deviations at any one induced pressure about the mean at that pressure was larger than the variance due to deviations about the means of the various induced pressures. This suggested the possibility that the observations on the different eyes were not homogeneous.

In order to investigate this possibility a separate analysis of variance was carried out taking into account the fact that eleven different eyes had been measured. The results of this procedure are summarized in Table 2. There is evidence, for both instruments, of significant differences from one experiment to the next (scleral tonometer $F = 32.24$, $df = 10,165$: corneal tonometer $F = 2.97$, $df = 10,165$). How can one account for this?

One possibility is that there are significant slope changes from one experiment to the next with each instrument. In order to investigate this one can test for the heterogeneity of slopes. For the corneal tonometer $F = 30.78$, $df = 10,154$ and for the scleral tonometer $F = 11.03$, $df = 10,154$. Clearly, for each instrument, the slopes do change significantly from experiments on one eye to those on another.

Despite the fact that significant heterogeneity between experiments exists with any one instrument, inspection of the variation removed by the common regressions suggests that the corneal tonometer is much less variable than the scleral tonometer since the common regression removes a much greater percent of the variation with the corneal tonometer than with the scleral tonometer. Similar data have been reported by others[5] and there seems little reason for doubting the generality of this conclusion.

Since analysis of variance shows that significant heterogeneity exists between experiments, a comparison of the sensitivity of each instrument by using the mean data of Figure 1 could perhaps be misleading. In order to compare the sensitivity of the two instruments it would be better to determine the slope of the best fitting line for each instrument in each eye examined. The analysis of the data in this manner is summarized in Table 3. Inspection of the data indicates that the slope of the best fitting line in each case is larger with the corneal tonometer than with the scleral tonometer.

TABLE 2

ANALYSIS OF VARIANCE ON 11 INDIVIDUAL EYES

	A. WOLFE			
	S.S.	D.F.	M.S.	F.
Individual regression	10,444.38	11	949.49	145.18
Common regression	8,431.30	1	8,431.30	1,289.19
Heterogeneity	2,013.08	10	201.31	30.78
Residual	1,006.14	154	6.54	
Total within experiments	11,450.52	165	69.40	
Between experiments	22,372.80	10	2,237.28	32.24
Total variation	33,823.32	175		
	B. SCHIØTZ			
	S.S.	D.F.	M.S.	F.
Individual regression	43,805.51	11	3,982.31	222.35
Common regression	41,830.98	1	41,830.98	2,335.62
Heterogeneity	1,974.53	10	197.453	11.025
Residual	2,757.79	154	17.91	
Total within experiment	46,563.30	165	282.20	
Between experiments	8,389.94	10	838.99	2.97
Total variation	54,953.24	175		

The Mann-Whitney U test can be applied to these data without assumptions regarding the distribution of the regression coefficients. This analysis shows that the slopes of the best fitting straight lines applied to the corneal tonometer are significantly higher ($p < 0.001$) than the slopes of the best fitting straight line of the data from the scleral tonometer. This supports the validity of the deductions made from the data in Figure 1.

TABLE 3

SLOPES OF INDIVIDUAL EXPERIMENTS ON 11 PIG EYES

Eye	Schiøtz	Rank	Wolfe	Rank
1	0.690	12	0.102	1
2	0.554	9	0.357	5
3	0.700	13	0.615	10
4	1.20	22	0.374	6
5	1.04	19	0.740	14
6	0.883	17	0.281	4
7	0.964	18	0.679	11
8	0.857	16	0.180	2
9	1.16	21	0.440	7
10	0.856	15	0.507	8
11	1.10	20	0.220	3
		$R_2 = 182$		$R_1 = 71$

$n_2 = 11$
$n_1 = 11$

$$U = n_1 n_2 + \frac{n_1(n_1+1)}{2} - R_1 = 121 + 66 - 71 = 187 - 71 = 116$$

$$U = n_1 n_2 + \frac{n_1(n_1+1)}{2} - R_2 = 187 - 182 = 5$$

p is less than 0.001 ($p = 0.001$ when $U = 15$ when $n_1 = n_2 = 11$)

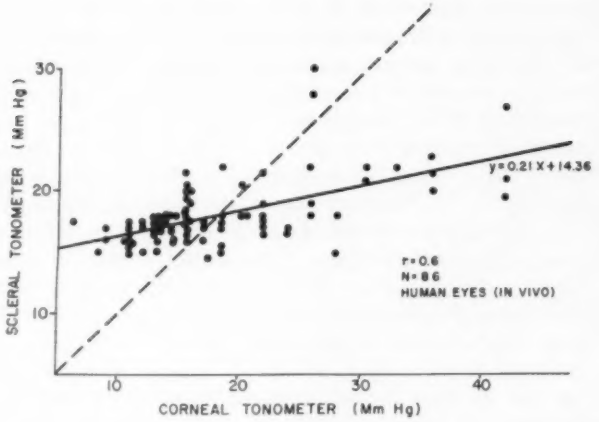

Fig. 2 (Hogg and Alpern). Scatter plot of measurements on 86 living human eyes showing the relation between measurement with corneal tonometer as compared to those with the scleral tonometer. The dotted line shows what relation is to be expected if the two instruments correlated perfectly.

Clearly, in pig eyes, the scleral tonometer is much less sensitive and the individual measurements much more variable than the corneal tonometer. What then, can be said about the application of the instruments to human eyes?

To answer this question measurements with both instruments were taken on a selected sample of clinical patients. Data was obtained on as wide a range of intraocular pressures as possible. Eighty-six eyes were measured with a pressure range, as measured with the corneal tonometer, of from 7.0 mm. Hg to 42.1 mm. Hg. The results from this study are plotted in Figure 2. It is clear from inspection of the data that the agreement between the two instruments is never very good. The range of the scleral tonometer in this same sample was only from 15 to 30 mm. Hg and neither of these two extremes differed from one another very much when their intraocular pressures were compared with the corneal tonometer. If the two instruments were perfectly correlated, the data should all cluster about the dotted line in the graph which has a slope of unity. Actually they cluster around a line with a slope of only 0.21. The eyes which have low values of intraocular pressure as measured with the corneal tonometer all give too high readings with the scleral instrument. Conversely those which have high values of intraocular pressure tend to show much too low values when measured with the scleral tonometer. These results are what one would anticipate in view of the experiments on pig eyes.

There is considerable reduction of sensitivity of the scleral tonometer as compared to the corneal tonometer. The readings from the two instruments do correlate to some extent; the correlation coefficient $r = +0.596$ is significantly larger than zero.* However, this is not sufficiently high to validate the scleral tonometer. This can be emphasized by pointing out that only 35.5 percent (that is, $r^2 = (0.596)^2$) of the variation in the measurements with this instrument can be attributed to factors which also will produce a variation in intraocular pressure as measured by the corneal tonometer.

Discussion

A tonometer should furnish data of the highest possible accuracy which may be used with family and personal histories, results of provocative tests, field examinations, tonographic data, and gonioscopic findings to facilitate the diagnosis and to assess the

* This is, however, considerably smaller than the value of +0.85 found by Talcott[3] on a sample about half as large. The discrepancy may be in part due to sampling differences and/or individual differences among instruments.

progress of the already diagnosed case of glaucoma. If an inaccurate instrument were to be depended upon, in screening examinations where tonometry may be solely relied upon for the detection of glaucoma, then the irrevocable changes of glaucoma could continue, even with the blessing of the unwitting user. The scleral instrument lacks sensitivity particularly in the critical range where tactile tensions lack sufficient discrimination, that is, in the range from 25 to 35 mm. Hg.

It is true that the sclera and cornea are nearly similar in consistency and that both contribute to the continuous fibrous envelope that encloses the essentially noncompressible fluid intraocular content. It would seem logical that a footplate of proper radius of curvature might be designed for an instrument which would function by measuring impressibility of the sclera. This possibility meets a serious obstacle, however, when one considers the episcleral tissues.

In order to emphasize this, the following experiment was carried out. Successive measurements were made of the intraocular pressure of one pig eye (which was maintained at a constant level of 29 mm. Hg) alternately with each instrument for 130 trials. The results of this experiment are plotted in Figure 3. It is evident that while the corneal measurements clustered about a horizontal line in a random way, the scleral measurements showed a continual decrement as the number of trials increased. Moreover, this decrement in scleral measurements was associated with an obvious impression of the footplate and plunger in the episcleral tissue after only the 12th scleral datum. No comparable impression ever appeared on the cornea even at the very end of the experiment. It is true that these conditions do not compare in any realistic way to those in which the instrument would ever be used in living eyes. On the other hand, living eyes do show variation in consistency, thickness, and vascularity of the episcleral tissues (as Sugar has already emphasized, in this regard[8]). Such individual differences should contribute to the variability of the scleral tonometer just as the change in the form of the episcleral tissues contributes to its variability in Figure 3.

In addition to these difficulties it should perhaps be pointed out that normal acts of convergence and palpebral spasm in the presence of normally sensitive conjunctiva[8] may also contribute to falsely elevated measurements of intraocular pressure with the scleral tonometer.*

Conclusions

The conclusions of this study may most

* The use of the Wolfe instrument held horizontally has inherent one further source of error. Because of its excess weight, the dial end tends to exert a torque on the sleeve which increases friction between the sleeve and the shaft.

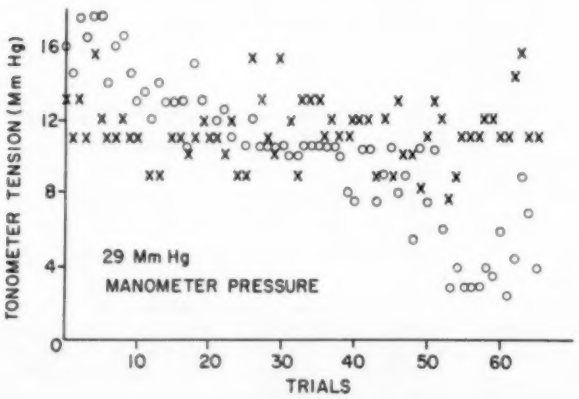

Fig. 3 (Hogg and Alpern). Measurements on one pig eye repeated for 130 trials alternately with the corneal (x) and scleral (open circles) tonometers. The pressure in the eye was maintained constant at 29 mm. Hg.

properly only be drawn with regard to the single instrument used in these experiments. The possibility exists, that other scleral tonometers would have fared better under such an analysis and that this particular instrument just happened to be a poor measuring device. While, if this were true, it would be sufficient reason for rejecting use of a device in which insufficient quality control in production does not insure that any given instrument will be clinically adequate, there is evidence that the matter is more serious than this.

Recently, after these experiments were completed, we became aware of the completely independent work of Cockburn[5] using another scleral tonometer. He compared the results with corneal tonometer readings in much the same way as that described in this present work. The results of his work were in complete agreement with those reported here.* There can be little doubt, therefore, that the generality of the conclusions must be considerably extended over that which would be otherwise permissible. It seems highly unlikely that the only instruments so far tested manometrically would not differ more widely in their characteristics if the factors which contribute to their low validity were not basic artefacts in the measuring procedure.

* Carter[6] also made a few manometric measurements on pig eyes with essentially the same results.

Summary

Manometric measurements on eleven pig eyes with corneal (Schiøtz) and scleral (Wolfe) tonometers showed that the latter was much less sensitive and much more variable than the former. Measurements on 86 living human eyes showed that the data from the two instruments are not sufficiently correlated ($r = +0.596$) to validate the scleral instrument. The reasons for the discrepancies in the readings of the two instruments are discussed.

University Hospital.

Acknowledgment

We would like to acknowledge the kind assistance of Prof W. J. Schull in the statistical analysis of the data and of Prof. H. F. Falls and Prof. David F. Bohr for many helpful suggestions.

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1228/142

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AUDITOR'S REPORT

Association for Research in Ophthalmology, Inc.

January 25, 1960

To the Members of the Board of Trustees
Association for Research in Ophthalmology, Inc.
10515 Carnegie Avenue
Cleveland 6, Ohio

Dear Sirs:

In accordance with the instructions of Dr. Lorand V. Johnson, Secretary-Treasurer of the Association for Research in Ophthalmology, Inc., I have examined the cash basis accounts of said association for the year ended December 31, 1959, and the recorded transactions for the year then ended. My examination was made in accordance with generally accepted auditing standards applicable to cash basis accounting and accordingly included such tests of the accounting records and other such auditing procedures as I considered necessary in the circumstances, except that I did not confirm unpaid dues directly with members.

Based upon my examination, I submit herewith my report consisting of the following exhibits:

A—Cash and securities in funds
B—Statement of cash receipts and disbursements
C—Membership dues collected
D—Summary of membership—by years

GENERAL COMMENTS

CASH IN BANK $ 5,503.12

The balance of $5,503.12 was in deposit with the Cleveland Trust Company, Euclid-105th Office, Cleveland, Ohio, and was verified by me by reconciliation and such other auditing methods I considered necessary. There were no outstanding checks or undeposited funds as of December 31, 1959.

SECURITIES $20,685.03

The securities shown in detail in Exhibit A, and being carried in the association's books for $20,685.03 are kept in safekeeping in a safety deposit box located at the Cleveland Trust Company, Euclid-105th Office, Cleveland, Ohio. These securities were examined by me and found to be in order.

At a meeting of the Board of Trustees held on October 11, 1959, it was voted that any and all members whose dues were in arrears for 1958 and 1959 would be written to again. Should the member fail to respond to such final communication then said member would be dropped for membership in the association.

Your attention is specifically directed to Exhibit B, "Statement of cash receipts and disbursements." This analysis shows that because of the publication of the additional "Friedenwald" supplement, the association's cash disbursements exceeded its cash receipts for the year under review. The association is already committed for an additional "Friedenwald" supplement for the year 1960 which it is anticipated will again result in a cash deficit for that year.

The records were found to be well kept and the financial transactions of the year properly authorized and recorded. Please accept my sincere thanks for the courtesy and co-operation given to me during my examination.

In my opinion, subject to the limitation that I did not confirm dues in arrears directly with members, the accompanying exhibits present fairly the fund balances of the Association for Research in Ophthalmology, Inc., as of December 31, 1959, and the receipts and disbursements for the year then ended, based on the recorded cash transactions, in conformity with generally accepted accounting principles. I do not feel that the exception referred to above, concerning dues arrearages, is sufficient to affect this opinion.

Respectfully submitted,
(Signed) WILLIAM J. SIEGEL.

Board of Trustees
Association for Research in Ophthalmology, Inc.
Cleveland, Ohio

Gentlemen:

I have reviewed the auditor's report for the fiscal year ending December 31, 1959. I approve of this report as a member of the auditing committee. (Signed) WERNER K. NOELL, M.D.

In reviewing the auditor's report of the Association for Research in Ophthalmology, Inc., for the year ending December 31, 1959, it appears to be in order, reflecting the cash and securities owned at the beginning and at the end of the year and the receipts and disbursements of cash for the year.

(Signed) GEORGE M. HAIK, M.D.

EXHIBIT A

CASH AND SECURITIES IN FUNDS

December 31, 1959

	General Fund	Proctor Medal Fund	Friedenwald Memorial Fund	Total
CASH:				
Cash in Bank 12-31-58	$11,480.40	—0—	$ 7,323.77	$18,804.17
Cash in Bank 12-31-59	5,503.12	—0—	—0—	5,503.12
Cash Decrease	$ 5,977.28	—0—	$ 7,323.77	$13,301.05
SECURITIES:				
$10,000.00 U.S. Treasury Bonds 2½%—1967-72	—0—	$10,184.63	—0—	$10,184.63
75 Shares Union Electric Co.— Value Date of Gift 7-30-56	—0—	—0—	$ 2,053.13	$ 2,053.13
10 Shares Ingersoll Rand Co.— Value Date of Gift 10-1-59	—0—	—0—	$ 782.50	$ 782.50
30 Shares E. I. DuPont de Nemours Cost 9-22-59	—0—	—0—	$ 7,664.77	$ 7,664.77
TOTAL SECURITIES	—0—	$10,184.63	$10,500.40	$20,685.03

SUMMARY

Cash in bank (per above)	$ 5,503.12
Securities (per above)	$20,685.03
TOTAL CASH AND SECURITIES—December 31, 1959	$26,188.15

EXHIBIT B

STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS

For the Year Ended December 31, 1959

CASH BALANCE—January 1, 1959:		
General Fund	$11,480.40	
Friedenwald Fund	7,323.77	
Proctor Medal Fund	—0—	$18,804.17
RECEIPTS—1959		
Interest Cambridge Savings Bank (Friedenwald Fund)		183.76
Dues collected—Exhibit C (General Fund)		13,376.15
Dividends—Union Elec. Co. (Friedenwald Fund)		118.50
Dividends—E. I. DuPont de Nemours (Friedenwald Fund)		75.00
Dividends—Ingersoll Rand Co. (Friedenwald Fund)		17.50
Banquet Proceeds (Proctor Fund)		780.00
U.S. Treasury Bond Interest (includes $250.00 applicable to 1958) (Proctor Fund)		500.00
Cash gift (Friedenwald Fund)		50.00
Total receipts—1959		$15,100.91
Total available cash		$33,905.08

DISBURSEMENTS—1959

For specific purposes:		
Publications (3 supplements)		$ 9,061.92
Friedenwald lectureship		500.00
Friedenwald plaques and engraving		698.42
Convention expenses		
Dinners		741.40
Programs, mailing, notices, etc.		608.30
Expenses—secretary-treasurer		250.00
Purchase of 30 shares E. I. DuPont de Nemours stock (Friedenwald Fund)		7,664.77
Total disbursements for specific purposes		$19,524.81
Balance of cash available for general purposes		$14,380.27
For general purposes:		
Stationery, supplies, printing		1,449.95
Postage		251.86
Office rental		515.04
Auditing		115.00
Telephone		202.36
Insurance: $5,000.00 position bond—Secy-Treas.		18.66
Board of Trustees' meeting—June and October		107.30
Contributions:		
American Committee on Optics & Visual Physiology		200.00
National Committee for Research in Ophthalmology and Blindness		500.00
Miscellaneous for rosters, supplements, etc.		329.34
Office Equipment—Verifax Copier		120.98
Midwinter National Meeting		89.50
Salary gross	$5,014.92	
Less taxes withheld	885.53	4,129.39
Withholding & FICA taxes paid[1]		761.67
International Council dues		86.10
Total disbursements for general purposes		$ 8,877.15
Balance of cash—December 31, 1959		$ 5,503.12

[1] Does not include payroll taxes for last quarter of 1959 in the total amount of $243.86.

EXHIBIT C

MEMBERSHIP DUES COLLECTED

For Year Ended December 31, 1959

1958			
14	Active Members @ $10.00	$ 140.00	
1	Educational Member @ $3.00	3.00	$ 143.00
1959			
993	Active Members @ $10.00	$9,930.00	
1	Active Member @ $10.15	10.15	
1	Active Member @ $15.00	15.00	
90	Educational Members @ $3.00	270.00	
75	Sustaining Members @ $25.00	1,875.00	
1	Sustaining Member @ $28.00	28.00	
1	Sustaining Member @ $100.00	100.00	$12,228.15
1960			
19	Active Members @ $10.00	$ 190.00	
1	Educational Member @ $3.00	3.00	
3	Sustaining Members @ $25.00	75.00	$ 268.00
1960 Provisional			
54	Active Members @ $10.00	$ 540.00	
9	Educational Members @ $3.00	27.00	
6	Sustaining Members @ $25.00	150.00	$ 717.00
1961			
1	Active Member @ $20.00	$ 20.00	$ 20.00
TOTAL DUES COLLECTED 1959			$13,376.15

EXHIBIT D

SUMMARY OF MEMBERSHIP—BY YEAR

To December 31, 1959

YEARS ENDED DECEMBER 31	TOTAL MEMBERS		
1959	1340[1]	1945	—[2]
1958	1190[1]	1944	283
1957	979	1943	—[2]
1956	930	1942	281
1955	822	1941	279
1954	815	1940	270
1953	713	1939	268
1952	672	1938	272
1951	556	1937	249
1950	509	1936	240
1949	474	1935	245
1948	422	1934	230
1947	306	1933	219
1946	324	1932	203
		1931	193
		1930	134

[1] Includes provisional members.
[2] Statistical information not available.

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Rumage, Joseph P.
Schoel, Robert E.

RUSTON
Harms, Harold H.

SHREVEPORT
Gray, Leon F.

MAINE

BANGOR
Osler, Jay K.

LEWISTON
Tchao, Jou S.

PORTLAND
Maier, Paul

WATERVILLE
Dennis, Richard H.
Hill, Howard F.

MARYLAND

BALTIMORE
Abrahams, Irwin W.
Brumback, Joseph E., Jr.
Duke, James R.
Hoover, Richard E.
Lawrence, Carteret
MacLean, Angus L.
Maumenee, Alfred E.
Naquin, Howard
Patz, Arnall
Pogell, Burton M.
Rowland, Louise S.
Wahlen, Henry E.
Wolff, Stewart M.
Wood, Ronald M.
Woods, Alan C.

BETHESDA
Chalfant, W. Paxson, Jr.
Gunkel, Ralph D.
Hart, William M.
Livingston, Robert B.
Macri, Frank J.
Peckham, Robert H.
Von Sallmann, Ludwig

CHEVY CHASE
Glew, William B.

MASSACHUSETTS

BOSTON
Allen, Henry F.
Andrews, John S., Jr.
Balazs, Endre A.
Beetham, William P.
Boruchoff, S. Arthur
Casten, Virgil C.
Chandler, Paul A.
Chisholm, Julian F., Jr.
Cogan, David G.
Donahue, Hugh C.
Dunphy, Edwin B.
Futterman, Sidney
Grant, W. Morton
Gunderson, Trygve
Heath, Parker
Jakus, Marie A.
Kern, Harold L.
Kinoshita, Jin H.
Kupfer, Carl
Kuwabara, Toichiro
Liebman, Sumner D.
Lo-Presti, Joseph J.
Martin, S. Forrest
Merola, Lorenzo O.
Murray, Edward S.
Regan, Charles D. J.
Schepens, Charles L.
Sloane, Albert E.
Snyder, John C.
Verhoeff, F. H.

BROOKLINE
Stone, William

CAMBRIDGE
Wald, George

CHESTNUT HILLS
Moorman, Lemuel T.

MEDFORD
Carpenter, Russell L.

NORWOOD
Ryan, William F.

SPRINGFIELD
Corcoran, George B., Jr.
Perlman, Arnold R.
Waugh, Richey L., Jr.

WORCESTER
Broggi, Richard J.
Holzer, William F.
Myers, Roscoe W.
Whitney, Percy T.
Yasona, Elton

MICHIGAN

ANN ARBOR
Alpern, Mathew
Falls, Harold F.
Fralick, F. Bruce
Henderson, John W.
Scharenberg, Konstantin
Smillie, John W.
Wolter, J. Reimer

BAY CITY
Heuser, Harold H.

DEARBORN
Bialik, Michael H.

DETROIT
Burroughs, Roswell G.
Crossen, Robert J.
Davies, Windsor S.
Dunlap, Henry A.
Frey, James L.
Guyton, Jack S.
Johnson, David S.
Kinsey, V. Everett
Kuck, John F., Jr.
Lepard, C. W.
Lerner, Leonard H.
Neeb, Walter
Olson, James A.
O'Rahilly, Ronan
Pugh, Howard C.
Reddy, D. Venkat
Ruedemann, A. D.
Ruedemann, A. D., Jr.
Schane, David
Scarney, Herman D.
Schimek, Robert A.
Sugar, H. Saul
Wachtl, Carl

FLINT
Barbour, Fleming A.
Rundles, Walter Z.

JACKSON
McGarvey, William E.
Wholihan, John W.

LINCOLN PARK
Flaherty, Norman W.
Wehr, Maurice B.

NILES
Moore, T. Scott

TRAVERSE CITY
Beall, John G.
Weih, Jack E.

WYANDOTTE
Barsky, David

YPSILANTI
Petrohelos, Manousos A.

MINNESOTA

DULUTH
Fellows, M. Fording
Hilding, Anderson C.

LITTLE FALLS
Johnson, Douglas L.

MINNEAPOLIS
Fink, Walter H.
Fowlks, W. L.
Friedman, Harry S.
Gruber, Louise
Halberg, Franz
Harris, John E.
Hoffman, Walter L.
Jerome, Bourne
McCannel, Malcolm A.
Sandt, Karl E.
Schwartz, Virgil J.
Shapiro, Irving
Simonson, Ernst
Walsh, Francis M.
Wendland, John P.

ROCHESTER
Bair, Hugo L.
Benedict, William L.
Henderson, John W.
Hollenhorst, Robert W.
Martens, Theodore G.
Ogle, Kenneth N.
Rucker, C. Wilbur
Sabin, Frederic C.
Sheard, Charles
Stein, Harold A.
Steinmetz, Rodney D.

ST. PAUL
Burch, Edward P.
Grant, Hendrie W.
Monahan, Robert H.
O'Kane, Thomas W.
Strate, Gordon E.

MISSISSIPPI

GREENVILLE
Gamble, Lyne S.

GULFPORT
Flagg, G. B.

JACKSON
Johnson, Samuel B.
Mayer, Leo L.

MISSOURI

CAPE GIRARDEAU
Wolff, Paul G.

CLAYTON
Bryan, James H.
Drews, Leslie C.
Freeman, David M.
Hildreth, H. Rommel
Israel, Milton R.

JEFFERSON CITY
Stauffer, Harry B.

KANSAS CITY
Calkins, Larry L.
Curran, Desmond
Eubank, William R.
Lemoine, Albert N., Jr.
McAlester, A. W., III
McKee, Joseph W.
McLeod, John
May, James W.

Miler, Wade H.
Padfield, Earl G., Jr.
Robison, James T., Jr.
Rufe, John R.
Shaad, Dorothy J.

MEXICO
Rouse, David M.

ST. LOUIS
Alvis, Edmund B.
Barnes, Charles R.
Becker, Bernard
Bisno, Daniel
Cibis, Paul A.
Constant, Marguerite A.
Enoch, Jay M.
Hartstein, Jack
James, William M.
Ley, Albert P.
Luedde, Philip S.
Mattis, Robert D.
Miles, Paul W.
Miller, James E.
Moses, Robert A.
Post, M. Hayward, Jr.
Rosenbaum, Harry D.
Sanders, T. E.
Schwartz, Frederick O.
Shah, Anwar
Shahan, Philip T.
Venable, Howard P.
Yamashita, Tsuyoshi

NEBRASKA

LINCOLN
Paulson, Hubert O.
Thomas, Richard L.

OMAHA
Alliband, George T.
Filkins, John C.
Gifford, Harold
Judd, John H.
Lipp, Frank E.
Mc Intire, Walden C.
Morrison, W. Howard
Rasgroshek, Robert H.
Swab, Charles M.
Truhlsen, Stanley M.

NEVADA

RENO
Magee, George R.

NEW HAMPSHIRE

BERLIN
Ingalls, Raymond G.

HANOVER
Auten, Hanford L.
Sullivan, Paul B.

NEW JERSEY

ASBURY PARK
Fisher, James A.

ATLANTIC CITY
Harley, Robison D.

BOUND BROOK
Levy, Abram

CAMDEN
Barnshaw, Harold D.
Meyer, George P.

EAST ORANGE
Cregar, John S.
Jaeckle, Charles E.

FAIRLAWN
Seligson, Alvin

HACKENSACK
Berke, Raynold N.

HADDONFIELD
Finley, John K.

JERSEY CITY
Cinotti, Alfonse A.
Nicholson, F. Peter

LONG BRANCH
Roberts, N. Craig

NEWARK
Adelman, Benjamin B.
Sherman, A. Russell

OCEAN CITY
Pettit, Paul H.

PASAIC
D'Amico, Thomas V.
Ehrenfeld, Edward
Lang, Richard E.
Silverstein, Arthur L.

PLAINFIELD
Samuels, S. Lawrence

PRINCETON
Abrams, Henry
Lascherer, E. Frederick

SHORT HILLS
Fonda, G. E.

SUMMIT
McAlpine, Paul T.

TRENTON
Balsis, Bernard A.
Murto, Robert E.
Sacks-Wilner, Erwin
Sharbaugh, George B.
Wilner, Arthur S.

NEW MEXICO

ALBUQUERQUE
Dillahunt, Jack A.
Schonberg, Albert L.

NEW YORK

ALBANY
Bedell, Arthur J.
Ward, Robert H.

AMSTERDAM
Fethke, Norbert

AUBURN
Platt, Edward S.

BAY SHORE
Bussey, Frank R.

BAYSIDE
Goodstein, Seymour

BINGHAMTON
Landers, Philip H.
Tobin, Henry L.
Walling, Henry G.
Werner, George B.

BRONX
Burman, Daniel
Fleischner, Alois L.

BROOKLYN
Ajello, Domenick A.
Beery, Edwin N.
Bodian, Martin
Bonadia, Calogero
Cholst, Mortimer
Evans, John N.
Fenton, Robert H.
Fink, Austin I.
Grassi, Anthony J.
Jampel, Robert S.
Landesberg, Jacques
Levine, George
Levitt, Jesse M.
Mandelbaum, Joseph
Rosenberg, Abner S.
Rosenthal, Benjamin C.
Sands, Abraham M.
Schwartz, Bernard

BUFFALO
Addington, Charles H.
Bennett, Arthur L.
Brennan, James W.
Buckheit, Rudolph G.
Cowper, Alexander R.
Fial, Edward A.
Fowler, James G.
Freeman, Sheldon B.
Higgs, Howard H.
Howard, William M.
Jones, W. Yerby
LeWin, Thurber
Luhr, John P.
Naples, Ange S.
Noell, Werner K.
Olmsted, K. Elizabeth Pierce
Reitz, Herbert R.
Schopp, Robert C.
Smallen, Benjamin

CORNING
Hoffman, Parker M.

ELMHURST
Flam, H. Leonard

ELMIRA
Boland, William T.
Voorhees, Charles H.

FAR ROCKAWAY
Goldsmith, Maximilian O.
Greenberg, Milton

FLUSHING
Kellerman, Leo D.

FOREST HILLS
Charap, Bertram W.

GARDEN CITY
Kieser, Carl E.

GLEN COVE
Boyd, James L.

GLEN FALLS
Mintz, Maxwell A.
Ryan, Edward P.

GREAT NECK
Branower, Gerald
Kaufman, Ira H.
Masor, Philip L.

ITHACA
Pritchard, Dale B.

JACKSON HEIGHTS
Presto, Ernest C.

JAMAICA
Douglas, Edward M.
Goldberg, Harry

JAMESTOWN
Franks, Myron B.

KEW GARDENS
Goldberg, Bernard

LANCASTER
Palmer, Milton A.

LAWRENCE
Wiener, Howard E.

LINDENHURST
Mason, David J.

LOCKPORT
Morgana, Dante J.

MASSAPEQUA
Bergmann, Robert B.

NEW HYDE PARK
Chatzinoff, Albert B.

NEW YORK
Bassen, Edward J.
Berens, Conrad
Berliner, Milton L.
Billet, Edwin
Bloomfield, Sylvan
Bonaccolto, Girolamo
Breakey, Arnold S.
Breinin, Goodwin M.
Bruce, Gordon M.
Byron, Herve M.
Campbell, Charles J.
Carroll, Frank D.
Carter, George Z.
Castroviejo, Ramon
Chambers, A. L., II
Chamlin, Max
Chang, Gilbert C. H.
Clark, Graham
Cohen, Irwin J.
Cole, Helen G.
Cole, John G.
Coles, Robert S.
Constantine, F. H.
Consul, Bishan N.
Curtin, Brian J. H.
Danforth, Edward P.
Day, Robert M.
Devi, Anima
DeVoe, Arthur G.
Dische, Zacharias
Doctor, Daniel W.
Dunlap, Edward A.
Dunnington, John H.
Epstein, Sidney S.
Esterman, Benjamin
Feinstein, Robert R.
Feldstein, Morris
Fernando, Antonio N.
Foote, Franklin M.
Fried, Joseph J.
Friedman, Benjamin
Gartner, Samuel
Givner, Isadore
Goodman, George
Goodside, Victor
Gordon, Dan M.
Gorin, George
Guy, Loren P.
Halberg, G. Peter
Hartshorne, Isaac
Jacobson, Jerry H.
Jones, Ira S.
Kahan, Edmund
Kara, Gerald B.
Katzin, Herbert M.
Keil, Francis C., Jr.
Kimmelman, David B.
Knapp, Arnold
Knapp, Arthur A.
Knapp, Phillip
Koppel, Zoltan I.
Kornzweig, Abram L.
Krohn, David L.
Kronenberg, Bernard
Krug, Joseph H.
Kumnick, Lillian S.
Lasker, Mary
Laval, Joseph
Levene, Ralph Z.
Linksz, Arthur
Lisman, Jack V.
Locatcher-Khorazo, Deborah
Loewenfeld, Irene E.
Lowenstein, Otto
Lubkin, Virginia
McDonald, George
McLean, John M.
Macnie, John P.
Mamelok, Alfred E.
Marcus, Arthur A.
Merriam, George R., Jr.
Nathaniel, Arthur
O'Connor, George R.
Paton, R. Townley
Payne, Brittain F.
Perera, Charles A.
Posner, Adolph
Proctor, Malvin
Regan, Ellen F.
Reese, Algernon B.
Rittler, M. Catherine
Roberts, Bernard A.
de Roetth, Andrew, Jr.
Romaine, Hunter
Sauer, John J.
Schachat, Walter S.
Schachne, Lewis
Schlossman, Abraham
Schneider, Julius
Schultz, Sigmund
Shafer, Donald M.
Smelser, George K.
Smith, Byron
Snyder, Stuart S.
Starr, Wilson C.
Sturman, Robert M.
Tabowitz, David
Teng, Chih Chiang
Theodore, Frederick H.
Troutman, Richard C.
Turtz, Arnold I.
Turtz, Charles A.
Tusak, Irvin A.
Wadsworth, Joseph A. C.
Webster, David H.
Weimar, Virginia L.
Weintraub, Alfred
Wexler, David
Wheeler, Maynard G.
Wise, George N.
Young, Morris

NIAGARA FALLS
Goetzman, Arthur C.

OLEAN
Sheldon, Maurice G.

PEARL RIVER
Vogel, Adolph W.

PEEKSKILL
Yasuna, Jules M.

PLATTSBURG
Siegel, Edward
Smith, Ronald P.

PORT CHESTER
Baum, Gilbert

POUGHKEEPSIE
Cohen, Irving

ROCHESTER
Caccamise, William C.
Gipner, John F.
Knoll, Henry A.
Lerman, Sidney
Pinsky, Abram
Sabey, Peter K.
Snell, Albert C., Jr.
Sullivan, Charles T.

ROCKVILLE CENTRE
Preefer, Charles

ROME
Reid, Frederick K.

ROSLYN HEIGHTS
Agatston, Howard J.
London, William

RYE
Simonton, John T.

SCHENECTADY
Polesny, Karel
Sykowski, Peter S.

STATEN ISLAND
Howard, Royal M.

SYRACUSE
Gillette, David F.
Katz, I. Herbert
McGraw, James L.
Marlow, Searle B.

UTICA
Valone, Richard J.

VALLEY COTTAGE
Cumming, Edith L. W.

WANTAGH
Esbin, Leo

WARSAW
Fountain, Newland W.
Leachman, John W.

WATERTOWN
Atkinson, Walter S.

WHITE PLAINS
Duncan, James A.

NORTH CAROLINA

ASHEVILLE
Odom, Robert E.

CHARLOTTE
Ghent, Thomas D.

DURHAM
Anderson, Banks
Draheim, Jerry W.
McPherson, Samuel D., Jr.
Stocker, Frederick W.

GOLDSBORO
Bizzell, James W.

WINSTON-SALEM
Holt, Lawrence B.
Perreten, Frank A.
Roberts, R. Winston
Weaver, Richard G.

NORTH DAKOTA

GRAND FORKS
Prochaska, Leonard J.

MINOT
Kohl, Darwin L.

OHIO

AKRON
Krichbaum, Franklin M.
Mathias, Daniel W.

ALLIANCE
King, George L.

CINCINNATI
Abrahamson, Ira A.
Abrahamson, Ira A., Jr.
Asbury, Mary K.
Asbury, Taylor
Ascher, Charles K. W.
Brown, Albert L.
Freemond, Alan S.
Ginsberg, Joseph
Kemper, Robert A.
Lyle, Donald J.
Nelson, Robert C.
Reid, Horace W.
Sakler, Barnet R.

CLEVELAND
Adams, Elliot Q.
Adelstein, Nelson J.
Ballintine, Elmer J.
Bennett, James E.
Binder, Hertha F.
Binder, Rudolf F.
Brandwan, Samuel R.
Budd, Francis X.
Chamberlain, Webb P., Jr.
Farkas, Tibor G.
Fleming, David G.
Gans, Jerome A.
Gans, Morris E.
Guth, Sylvester K.
Hardesty, Hiram H.
Hare, James
Harvey, Elmer F.
Hertner, John E.
Johnson, Lorand V.
Kazdan, Philip
Kennedy, Roscoe J.
Keyes, John E. L.
Kirk, Robert C.
Kohn, Howard D.
Kottler, Saul
Modrell, Robert W.
Nicholl, Russell J.
Phillips, Josephine D.
Rosner, Robert S.
Schwarz, Gerald T.
Smith, Clarence G.
Sperelakis, Nick
Thomas, Charles I.
Volk, David
Volk, Myron
Waitzman, Morton B.
Weekley, Robert D.
Wolpaw, Benjamin J.

COLUMBUS
Barton, Stanley L.
Battles, Morris L.
Ellerbrock, Vincent J.
Fry, Glenn A.
Havener, William H.
Hebbard, Frederick W.
Knox, George W.
Lipetz, Leo E.
Magnuson, Robert H.
Makley, Torrence A.
Perry, Claude S.
Prince, Jack H.
Stine, George T.
Suie, Ted
Westheimer, Gerald

DAYTON
Insel, Herman H.
Thomas, Edward R.

DOVER
Wherly, Harold

KENT
Van Dyke, Donald P.

LAKEWOOD
Ellenberger, Carl

MARION
Greetham, James S.

MASSILLON
Rummel, William D.

PARMA
Graham, John H.

SEVEN HILLS
Gilger, Anita P.

STEUBENVILLE
Stein, Lester

TOLEDO
Ravin, Louis C.
Roberts, J. L.
Schmerl, Ernest
Skow, John D.
Steinberg, Bernhard
Taylor, Frank W.
Vesey, Frank A.

UNIVERSITY HEIGHTS
Weinberg, Herman C.

WARREN
Chickering, Donald H.
Thomas, John H.

YOUNGSTOWN
Bloomberg, Louis
Evans, William H.
Ruth, Paul E.
Sovik, William E.
Stertzbach, C. W.

ZANESVILLE
Letson, Holton C.

OKLAHOMA

OKLAHOMA CITY
Robertson, E. Norris, Jr.

TULSA
Lee, Otis S.
Ozment, Thomas L.

OREGON

ASTORIA
Browning, Charles W.

COOS BAY
Flanagan, Roger M.

EUGENE
Christoferson, Kent W.
McCallum, George C.

PORTLAND
Allen, Aurelia J.
Burns, Robert P.
Butler, J. B. V.
Christensen, Leonard
Heinrich, Daniel
Markley, Richard E.
Reeh, Merril J.
Swan, Kenneth C.
Talman, Ellen L.
Tanner, K. Nolen
Taylor, E. Merle

SALEM
Hammerstad, Lynn M.

PENNSYLVANIA

ALLENTOWN
Beitel, Robert J., Jr.
Phillips, Samuel A.
Shoemaker, Robert E.

BEDMINSTER
Duane, Thomas D.

BELLEFONTE
Covey, John K.

BERWICK
Ross, Joseph V. M.

BETHLEHEM
Ojers, Gaylord W.

BRYN MAWR
McGavic, John S.

BUTLER
Brown, James W.

DANVILLE
Mahood, A. W.

EASTON
Jacobius, Henry F.

ELKINS PARK
Apt, Leonard

ERIE
Alberstadt, Norbert F.
Calabrese, Arthur B.

GLENSHAW
Shaw, Harry E.

GREENSBURG
Baldwin, Gertrude W.
Brant, Carl E.

HARRISBURG
Eisenberg, I. J.
Martz, George E.

HAZLETON
Koven, Arthur L.

HOMESTEAD
Sinclair, Stephen G.
Yatzkan, David N.

KITTENNING
Yockey, Robert H.

LANCASTER
Ripple, Paul H.

LANSDALE
Carmichael, Paul L.

LATROBE
Mather, Homer R., Jr.

MCKEES ROCKS
Terner, Irwin S.

PHILADELPHIA
Adler, Francis H.
Ashodian, Mila J.
Askovitz, Samuel I.
Belmont, Owen
Blazar, Howard A.
Brav, Solomon S.
Cohen, Louis B.
Cowan, Alfred
DeLong, Samuel L.
Ellis, Richard A.
Frayer, William C.
Gettes, Bernard C.
Goren, Seymour B.
Green, Harry
Gibson, Glen G.
Hallett, Joseph W.
Hedges, Thomas R., Jr.
Krewson, William E., III
Krishna, Narenda

Leopold, Irving H.
Lipsius, Edward I.
Lutman, Frank C.
McDonald, P. Robb
Mullen, Carroll R.
Naidoff, David
Reese, Warren S.
Scheie, Harold G.
Sery, Theodore W.
Spaeth, Edmund B.
Spaeth, Philip G.
Trueman, Robert H.
Waldman, Joseph
Weaver, Harry S., Jr.
Wolkowicz, Michael I.
Zentmayer, William

PITTSBURGH

Berk, Myles M.
Billings, Robert J.
Black, Henry H.
Bronk, Henry N.
Davies, Robert H.
Dunbar, John C.
Evans, Thomas M.
Everett, William G.
Geeseman, George R.
Goldberg, Sol
Hoffman, Franklin D.
Krieger, A. A.
Lehman, Robert N.
Linn, Jay G., Jr.
Linn, Jay G., Sr.
McCaslin, Murray F.
Novak, Joseph F.
Rohm, Robert F.
Shin, Ernest H.
Statti, Louis W.
Steinberg, Abraam
Thorpe, Harvey E.
Weisser, Charles W.
Wickerham, Earl P., Jr.
Wolken, Jerome J.

READING

Craig, Paul C.
Quereau, James V. D.
Souders, Benjamin F.

SAUDERTON

Capriotti, Octavius A.

SEWICKLEY

Henry, Edgar S., Jr.

SHARON

Bloomenthal, Sanford R.
Riddle, Ransford J.
Snyder, M. Wilson

TARENTUM

Kennerdell, Edward H.

UPPER DARBY

Kennedy, Patrick J.

WARREN

Ball, William L.

WASHINGTON

Tibbens, George F.

RHODE ISLAND

PROVIDENCE

Ross, Milton G.
Stephens, H. Frederick

SOUTH CAROLINA

BEAUFORT

Sullivan, John J.

CHARLESTON

Croffhead, George S.
Vallotton, William M.

FLORENCE

Stokes, Julius H.

GREENVILLE

Brown, Robert A.
Jervey, James W., Jr.

SOUTH DAKOTA

ABERDEEN

Rudolph, Edward A.

HURON

Kilpatrick, William R. J.

RAPID CITY

Palmerton, E. S.

YANKTON

Willcockson, Thomas H.

TENNESSEE

CHATTANOOGA

Arnold, I. Lee

JOHNSON CITY

Campbell, E. Malcolm

KINGSPORT

Boles, James H.

KNOXVILLE

Benedict, Walter H.
Leach, Robert S.

MEMPHIS

Deutsch, Alice R.
Krause, Arlington C.
Lewis, Phillip M.
Rychener, Ralph O.

NASHVILLE

Bounds, George W., Jr.
Driver, L. Rowe
Lawrence, G. Allen
Patterson, John W.

TEXAS

ABILENE

Seale, Hubert J.

AMARILLO

McKay, Edward D.
Murphy, Weldon O.

AUSTIN

Davidson, Morris
Hilgartner, H. L.
Key, Samuel N., Jr.
Legett, Carey, Jr.

BEAUMONT

Caldwell, Pearson C.

CORPUS CHRISTI

Gill, E. King
Stevenson, Roger

DALLAS

Browning, Carroll W.
Byers, Jerome L.
Cary, Edward H.
Grafton, Edwin G.
Melton, Carlton E., Jr.
Quinn, Lester H.
Thomas, Maxwell

EL PASO

Schuster, Stephen A.

FORT HOOD

Chambers, Arthur L., II

FORT WORTH

Beasley, Harold
Conner, William C.
Fleming, T. C.
McKenzie, Walten H.
Merrill, David L.
Maxwell, Earl

GALVESTON

Gingrich, Wendell D.
Potter, William B.
Robertson, Gaynelle

HOUSTON

Daily, Louis, Jr.
Daily, Ray K.
Dukes, Charles D.
Feldman, Gerald I.
Girard, Louis J.
Goar, Everett L.
Griffey, Edward W.
Leigh, Richard, Jr.
Vanzant, Thomas J.

MCALLEN

Frink, Berton F.

PORT ARTHUR

Heare, Louis C.

SAN ANTONIO

Matthews, John L.
Mims, James L., Jr.
Weixel, Francis X.

TEMPLE

Veirs, Everett R.

UTAH

PROVO

Oaks, Lewis W.

SALT LAKE CITY

Muir, Everett B.
Smith, Homer E.
Wood, Donald C.

VERMONT

BURLINGTON

Cunningham, John C.
Hanna, Calvin

VIRGINIA

ARLINGTON

Mitchell, Robert H.

CHARLOTTESVILLE

Brunish, Robert
Burton, Edwin W.
Spence, George

DANVILLE

Byerly, Baxter H.

LYNCHBURG

Hobbs, Frank I.

NORFOLK

Crockett, Douglas H.

QUANTICO

McArtor, James R.

RICHMOND

Geeraets, Walter J.
Guerry, duPont, III
Rein, Walter J.
Sheppard, L. Benjamin
Wiesinger, Herbert
Williams, Richard K.

ROANOKE

Stone, W. Conrad
Young, Charles A., Jr.

WINCHESTER
McGuire, William P.

WASHINGTON

BELLEVUE
Milam, Daniel F., Jr.

BELLINGHAM
Kaiser, Robert F.

BREMERTON
Benson, Clifton E.

LONGVIEW
Hill, Robert V.

RENTON
Maynard, Robert E.

PULLMAN
Young, Francis A.

SEATTLE
Hargiss, James L.
Hungerford, Louis N.
Jensen, Carl D. F.
Lyda, Wood
Peter, Philip A.

SPOKANE
Gates, Charles L.
Richter, William C.
de Roetth, Andrew F. M.

TACOMA
Ward, James F.

WALLA WALLA
Hogenson, Clifford D.
Stevens, Ralph W.

WENATCHEE
Miller, Claude K.

WEST VIRGINIA

HUNTINGTON
Polan, Charles M.

MORGANTOWN
Ryan, Ralph W.

PARKERSBURG
Shupala, Edward

PRINCETON
Ball, Donald N.

WISCONSIN

LA CROSSE
Mansheim, Bernard J.

MADISON
Berger, John V., Jr.
Buesseler, John A.
Davis, Matthew D.
Engerman, Ronald L.

MILWAUKEE
Blankstein, Samuel S.
Bolger, James V.
Carl, E. Franklin
Gaynon, Irwin E.
Hitz, John B.
Holm, Arvid G.
Schalmo, E. H.

MONROE
Mings, Dwain E.

NEENAH
Kirchgeorg, Clemens

RACINE
Kadin, Maurice

HAWAII

HONOLULU
Holmes, William J.
Pang, Herbert G.
Pinkerton, Ogden D.

KAHULUI
Kushi, Harold S.

PUERTO RICO

SANTURCE
Buxeda, Roberto
Margarida, Carlos J.

CANADA

ALBERTA

EDMONTON
Duggan, John W.
Marshall, M. R.

MANITOBA

WINNEPEG
Elvin, Norman L.

NOVA SCOTIA

HALIFAX
Quigley, John H.

ONTARIO

KINGSTON
Rosen, David A.

LONDON
Dyson, Charles

NIAGARA FALLS
Eager, R. F.

OTTAWA
Fraser, Wilmur F.

TORONTO
Basu, Prasanta K.
Bishop, Harding E.
Elliot, Alfred J.
Levitt, Herbert
McCulloch, Clement
MacDonald, Roy K.
Ormsby, Hugh L.
Shusterman, Morris

QUEBEC

MONTREAL
Alexander, Benjamin
Boxer, Louis
Brault, Jules
Cloutier, Roland
Langman, Jan
Locke, John C.
Viger, R. J.

BRITISH COLUMBIA

VANCOUVER
Irving, John A.
Mallek, Howard
Ragan, John D.

VICTORIA
Wiggins, Robert L.

CENTRAL AND LATIN AMERICAN COUNTRIES

ARGENTINA

CORDOBA
Urrets-Zavalia, Alberto, Jr.

BRAZIL

BAHIA
de Andrade, Cesario

BELO HORIZONTE
Dasilva, Antonio I.

COSTA RICA

SAN JOSE
de la Cruz, Edgar

CUBA

HAVANA
Ferrer, Horation

MEXICO

MEXICO CITY
Camacho, Enriqueta
Puig-Solanes, M.
Wudka, Enrique

PERU

LIMA
Barrere, Luciano E.
Raffo, Julio C.

VENEZUELA

CARACAS
Grom, Edward

PHILIPPINE ISLANDS

MANILA
Arribas, Neva P.
De Ocampo, Geminiano

QUEZON CITY
Quilala, Francisco V.

BELGIUM

ANTWERP
Neetens, Adolphe

GHENT
Francois, Jules

ENGLAND

LONDON
Duke-Elder, Lady Phyllis
Duke-Elder, Sir Stewart

ISRAEL

JERUSALEM
Auerbach, Edgar L.

ITALY

GENOVA
Grignolo, Antonio

JAPAN

FUKUOKA-SHI
Taniguchi, Yoshiaki

HONGO
Hagiwara, Hogara

SPAIN

MADRID
Carrasquillo, Honorio F.

SOUTH AFRICA

JOHANNESBURG
Taylor, Israel B.

SWITZERLAND

GENEVA
Blum, John

ZURICH
Huber, Alfred